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Targeting endoplasmic reticulum proteostasis in liver fibrosis: From signaling mechanisms to therapeutic opportunities

Yawei Kong, Zhengyang Chen, Zhentian Nie, Wei Chen *

Multiscale Research Institute of Complex Systems, Fudan University, Shanghai 200433, China

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ABSTRACT

Liver fibrosis, a progressive consequence of chronic liver disease, is characterized by excessive extracellular matrix (ECM) deposition and persistent inflammation. It poses a substantial global health burden, particularly among individuals with obesity, excessive alcohol intake, or chronic viral hepatitis. Increasing evidence suggests that endoplasmic reticulum (ER) stress plays a critical role in fibrogenesis by disrupting cellular homeostasis and activating pathological signaling pathways. This review offers a comprehensive overview of the mechanisms driving liver fibrosis, with a particular emphasis on ER stress-associated pathways, including ER-associated degradation (ERAD), the unfolded protein response (UPR), and autophagy. We further discuss the impact of chronic ER stress on hepatocytes, hepatic stellate cells (HSCs), and Kupffer cells (KCs), emphasizing their roles in fibrosis progression. Finally, we explore therapeutic strategies targeting ER stress as potential antifibrotic interventions, providing novel insights into the treatment of liver fibrosis.

1. Introduction

Liver fibrosis, also known as hepatic fibrosis, represents a significant global health burden, affecting millions of individuals worldwide[1,2]. The most notable characteristics of liver fibrosis are chronic inflammation and the excessive deposition of extracellular matrix (ECM) proteins [3], leading to the formation of scar tissue that replaces normal, damaged liver tissue and may ultimately contribute to liver failure[4]. Liver fibrosis arises from chronic liver injury caused by a range of factors, including viral infections (e.g., hepatitis B and C), metabolic diseases (e.g., non-alcoholic fatty liver disease, NAFLD, now referred to as metabolic dysfunction-associated steatotic liver disease, MASLD), alcohol consumption, and autoimmune diseases[5]. Following chronic liver injury, a cascade of events unfold, including an inflammatory response, fibrogenesis, and either fibrosis regression or progression to more severe conditions such as cirrhosis, liver failure, and even hepatocellular carcinoma (HCC)[6]. However, recent technological advances [7–11], such as single-cell RNA sequencing, have revealed that the

Abbreviations: ECM, Excessive extracellular matrix; ER, endoplasmic reticulum; ERAD, ER-associated degradation; UPR, unfolded protein response; HSCs, hepatic stellate cells; KCs, Kupffer cells; NAFLD, non-alcoholic fatty liver disease; MASLD, metabolic associated steatotic liver disease; HCC, hepatocellular carcinoma; CLDs, chronic liver diseases; T2DM, type 2 diabetes; MASH, metabolic-associated steatohepatitis; LSECs, liver sinusoidal endothelial cells; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species; TGF-β, transforming growth factor-beta; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors; AI, artificial intelligence; IRE1, inositol-requiring enzyme 1; PERK, protein kinase RNA-like ER kinase; ATF6, activating transcription factor 6; XBP1, RE1 activates X-box binding protein 1; EIF2α, eukaryotic initiation factor 2α; RER, interconnected rough ER; SER, reticulated smooth ER; ER-E3s, RIDD, ER-membrane-embedded ubiquitin ligasesIRE1α-dependent regulated IRE1 decay; UORFs, upstream open reading frames; ATF4, activating transcription factor 4; TRB3, tribbles homolog 3; CHOP, C/EBP homologous protein; S1P, site-1 protease; S2P, site-2 protease; ATGs, autophagy-related proteins; LC3, light chain 3; P62/SQSTM1, autophagic substrate p62/Sequestosome-1; FFAs, free fatty acids; TGs, triglycerides; SFAs, saturated fatty acids; VLDL, very-low-density lipoprotein; PLA2, phospholipase A2; LPC, decreases lysophosphatidylcholine; CRE, cis-regulatory element; CTH, GSH, cystathionine γ-lyaseglutathione; GPX4, glutathione peroxidase 4; PA, palmitic acid; DR5, death receptor 5; GSDMD, gasdermin D; NLR, NOD-like receptor; ASC, apoptosis-associated speck-like protein; TLR, Toll-like receptor; α-SMA, α-smooth muscle actin; TXNDC5, thioredoxin domain containing 5; ATG7, autophagy-related protein 7; TANGO1, SERCA2, Transport and Golgi Organization 1sarcoplasmic/ER calcium ATPase 2; EMT, epithelial-mesenchymal transition; IRI, ischemia/reperfusion injury; TREM-1, triggering receptor expressed on myeloid cells 1; Nogo-B, RTN4B, Reticulon 4B; ALD, alcoholic liver disease; KIRAs, kinase-inhibiting RNase attenuators; ISR, integrated stress response; TUDCA, tauroursodeoxycholic acid; 4-PBA, 4-phenylbutyric acid.

* Corresponding author.
E-mail address: w_chen16@fudan.edu.cn (W. Chen).

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progression of liver fibrosis is not a simple linear process but rather involves a complex and interconnected network. Understanding the underlying mechanisms of liver fibrosis can facilitate the identification of effective targets for antifibrotic therapies.

Recent research has increasingly emphasized the role of cellular stress[12,13], particularly ER stress[14–20], in the pathogenesis of liver fibrosis. ER stress refers to the accumulation of misfolded or unfolded proteins in the ER, triggering the unfolded protein response (UPR)[21]. While mild ER stress contributes to restoring protein homeostasis through defense mechanisms such as ER-associated degradation (ERAD), the UPR, and autophagy, whereas excessive and chronic ER stress leads to hepatocyte death[22,23] and the activation of Kupffer cells and hepatic stellate cells (HSCs)[24], which are strongly associated with liver damage, inflammation, fibrosis, and even HCC[25]. Early-stage liver fibrosis has been confirmed to be reversible, and two key strategies for promoting its regression have been identified: inhibiting hepatocyte apoptosis, which exacerbates liver damage, and promoting the apoptosis and inactivation of HSCs, which contribute to the accumulation of ECM. Given its critical role, targeting ER stress represents a promising strategy for promoting liver fibrosis regression.

Currently, effective pharmacological treatments for liver fibrosis remain lacking, and existing diagnostic methods typically detect the condition only in advanced stages, when disease reversal is challenging and liver transplantation becomes the sole treatment option. In terms of diagnosis, recent research has focused on liver fibrosis screening[26,27], elastography techniques[28–30], and the development of non-invasive biomarkers[31–33], aiming to achieve precise and early-stage detection. These advancements seek to minimize the risks associated with liver biopsy while improving diagnostic accuracy. Early detection of liver fibrosis during its reversible phase could facilitate timely interventions, such as lifestyle modifications[34] or pharmacological treatments, to halt or even reverse disease progression. In the realm of treatment, growing attention has been directed toward nano-drug delivery systems[35,36] to enhance the targeted delivery and therapeutic efficacy of potential drugs. Furthermore, extensive research efforts are dedicated to identifying novel therapeutic targets to aid in the development of effective clinical treatments for liver fibrosis. Recent studies[16,26,27] have outlined the role of ER stress in liver diseases. In this Review, we present a novel perspective by integrating recent advances in the cellular landscape of liver fibrosis, with a particular focus on how ER stress differentially influences key hepatic cell types, including hepatocytes, Kupffer cells, and hepatic stellate cells. We further emphasize the translational potential of cell type–specific ER stress targeting and summarize emerging small-molecule modulators and therapeutic strategies. This cell-type oriented discussion offers new insights into the pathogenesis and treatment of liver fibrosis that are not extensively covered in previous reviews.

2. Liver fibrosis

2.1. Epidemiology and clinical features

Liver fibrosis is increasingly recognized as a critical determinant of patient prognosis and mortality in chronic liver diseases (CLDs), posing a significant global health concern. Epidemiological studies estimate that the global prevalence of significant liver fibrosis is approximately 7.3 %, advanced liver fibrosis is around 3.3 %, and cirrhosis affects nearly 1.2 % of the population[1,2]. The incidence is significantly higher in men than women and exhibits a notable age-dependent increase[1,2]. Chronic and progressive liver fibrosis is the primary driver of liver cirrhosis, leading to irreversible hepatic damage and severe complications, including hepatic encephalopathy, ascites, and portal hypertension, along with a markedly increased risk of HCC. The progression from fibrosis to cirrhosis typically spans two to three decades. Strikingly, over 90 % of HCC cases arise in cirrhotic livers, with cirrhosis and its associated complications serving as the leading causes of liver-related mortality worldwide[28].

Liver fibrosis arises from a variety of causes, including metabolic disorders, viral infections, excessive alcohol consumption, autoimmune diseases, and cholestatic and genetic conditions[5,28]. Metabolically, the most common factors contributing to MASLD, which can progress to liver fibrosis, are type 2 diabetes (T2DM) and obesity. A large, multicenter cohort study revealed that, compared with non-T2DM patients, those with T2DM exhibited a significantly higher cumulative incidence of fibrosis progression at 4, 8, and 12 years (hazard ratio: 1.69), underscoring T2DM as a key accelerator of fibrosis progression[29]. A meta-analysis of 151 studies encompassing 101,028 individuals revealed that the majority of obese individuals had MASLD, with approximately 33 % progressing to metabolic-associated steatohepatitis (MASH). Furthermore, among patients with MASLD, approximately 21 % of obese individuals had clinically significant liver fibrosis, while around 7 % developed advanced liver fibrosis[30]. Notably, studies indicate that the incidence of advanced liver fibrosis increases significantly with rising body mass index (BMI)[31], highlighting a strong association between obesity severity and fibrosis progression. Besides, the population with excessive alcohol consumption (defined as >21 drinks per week for men and >14 drinks per week for women), along with those suffering from alcohol disorders, is at significantly higher risk for developing alcohol-related liver disease, particularly cirrhosis[32,33]. Viral hepatitis also remains a major contributor to liver fibrosis. These risk factors can act independently or synergistically to accelerate the progression of liver fibrosis. For instance, a super-additive interaction exists between elevated BMI and alcohol consumption, where even low levels of alcohol intake may exacerbate fibrosis progression in MASLD patients[34]. While eliminating these risk factors may aid in the early-stage intervention and improvement of liver fibrosis, its effectiveness in advanced liver diseases, such as cirrhosis, remains limited. The details regarding treatment strategies for liver fibrosis will be discussed later.

2.2. Pathophysiology and mechanisms

The liver is a vital organ responsible for energy homeostasis, metabolism, and immune regulation. Its remarkable regenerative capacity allows it to recover even after severe acute injury or partial resection [12,35]. However, prolonged chronic damage can compromise this repair mechanism, ultimately resulting in fibrosis and cirrhosis. Pathologically, liver fibrosis represents a dynamic and multifaceted wound-healing response, characterized by the excessive deposition of ECM components, primarily collagen types I and III. This pathological remodeling gradually replaces damaged liver tissue, leading to progressive deterioration of hepatic architecture, function, and regenerative capacity[36]. The progression of liver fibrosis is governed by a complex interplay of cellular and molecular mechanisms involving hepatocytes, cholangiocytes, inflammatory cells (such as Kupffer cells, monocytes and T cells), liver sinusoidal endothelial cells (LSECs), and hepatic stellate cells (HSCs). These interactions are further modulated by a sophisticated network of signaling pathways and regulatory factors. Fig. 1 provides an overview of the mechanisms underlying liver fibrosis, while Table 1 outlines the specific roles of different cell types in this pathological process. A deeper understanding of the mechanisms underlying liver fibrosis is essential for identifying antifibrotic targets and developing effective therapeutic interventions.

2.2.1. Liver homeostasis

Under physiological conditions, hepatocytes—constituting approximately 80 % of the liver's mass[37]—serve as the principal parenchymal cells responsible for executing vital metabolic, synthetic, and detoxification functions. The vast majority of hepatocytes remain in a quiescent state, undergoing minimal proliferative activity, with only a small subset capable of limited replication[37,38]. Cholangiocytes, which are primarily involved in maintaining bile acid homeostasis, also

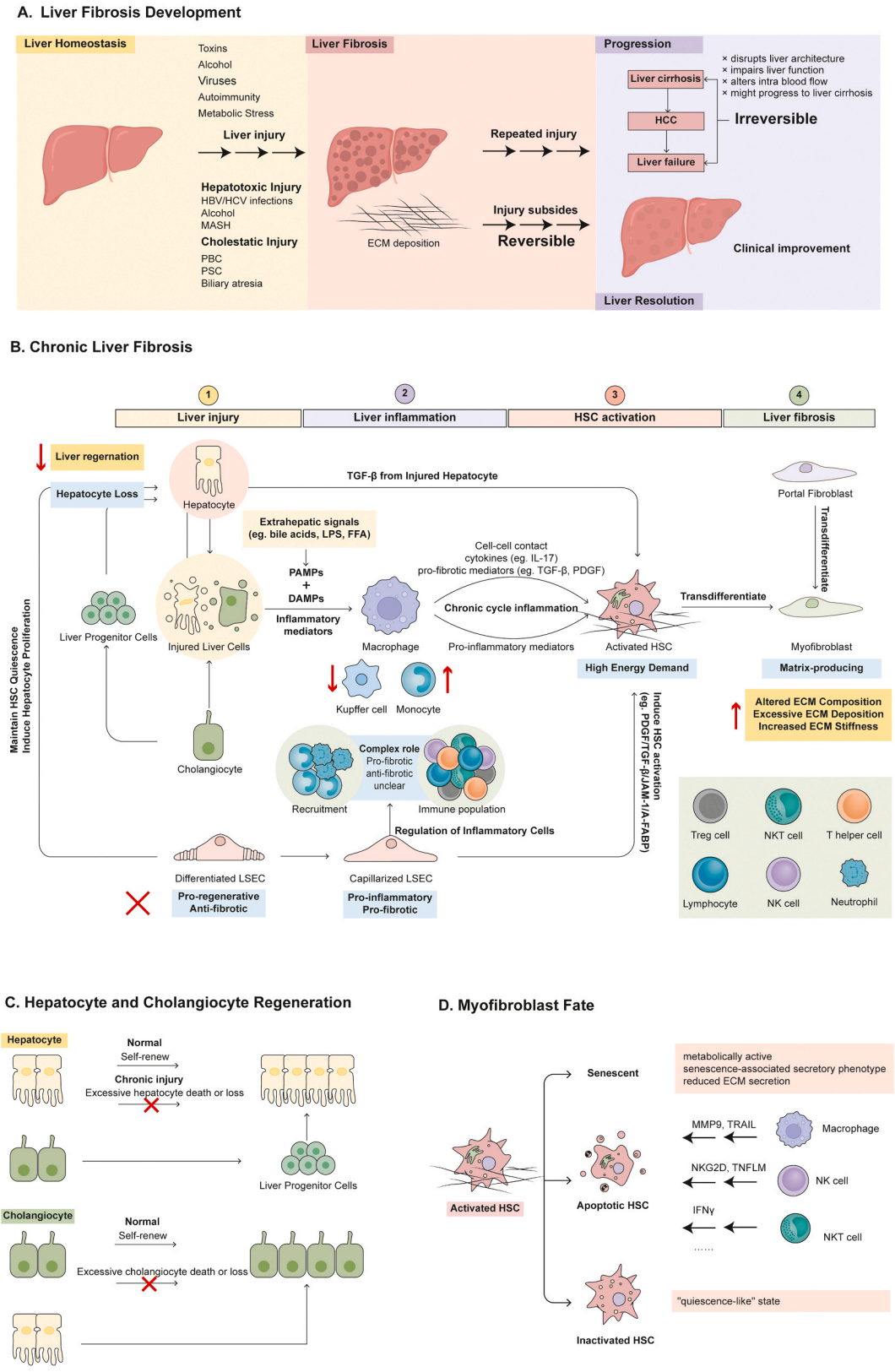


Fig. 1. Mechanisms of liver fibrosis progression and cell fate regulation. A: the disease progression of liver fibrosis, from acute injury to chronic fibrosis, potentially leading to cirrhosis or hepatocellular carcinoma. B: mechanisms underlying chronic liver fibrosis, highlighting the activation, intercellular communication, and feedback loops among hepatocytes, immune cells, hepatic stellate cells, and fibroblasts, which together drive fibrosis progression under persistent injury. C: the regenerative mechanisms of hepatocytes and cholangiocytes. Under normal or mild injury conditions, both can self-renew; under severe damage, bidirectional transdifferentiation occurs between the two cell types to sustain regeneration. D: Myofibroblast fate decisions during fibrosis resolution, including senescence, inactivation, and apoptosis.

Table 1
Cell types involved in the progression of liver fibrosis.

Cell Type	Description	Liver homeostasis	Acute liver injury	Chronic liver fibrosis	Fibrosis regression	Ref
Hepatocytes	Main parenchymal cells (~80 % of liver mass); perform metabolic, detoxification, and synthetic tasks	Largely quiescent; self-renewal via *TERT*^{hi} and *AXIN2*^+cells; regulated by HGF/EGFR	Proliferation to restore tissue	Senescence-driven loss; limited proliferation; *SOX9*^+ periportal hepatocytes contribute to regeneration	Broad proliferation; *AXIN2*, *LGR5*, and *LGR4* upregulated; regeneration from hybrid hepatocytes	[36–38]
Cholangiocytes (BECs)	Epithelial cells lining bile ducts (~3 % of liver mass); modify and transport bile	Self-renewal via *TET1* and bile acid–induced YAP activation	Proliferation increases	Expansion in ductular reaction; limited hepatocyte regeneration via biliary-derived cells	Continued BEC proliferation and bile acid secretion; Wnt-driven transdifferentiation into hepatocytes; Notch supports BEC expansion	[37,38, 210]
Liver Sinusoidal Endothelial Cells (LSECs)	Fully differentiated endothelial cells with fenestrated structure; lack basement membrane	Regulate hepatocyte proliferation; control Kupffer cell distribution and hepatic immune tolerance; maintain HSC quiescence	Activated by pro-angiogenic signaling	Capillarization, reduced fenestrae porosity; induce HSC activation; pro-fibrotic and pro-inflammatory	Activated; contribute to fibrosis regression by modulating HSC and hepatocyte function	[36,42, 43,48]
Kupffer Cells (KCs)	Liver-resident macrophages (~15 % of liver mass); involved in immune surveillance and homeostasis	Scavenge microbes and damaged cells; regulate immune tolerance and control gut-derived pathogen entry	Depletion of KCs impairs regenerative and immune functions	Depletion of KCs contributes to reduced immune function and exacerbated fibrosis	\	[3,5,37, 40]
Monocytes	Immune cells that migrate from the bone marrow to the liver	Remain quiescent in liver homeostasis; contribute to immune surveillance	Activation of monocytes in response to injury	Activated monocytes contribute to pro-inflammatory response and fibrosis progression	\	[3]
Macrophages	Kupffer cells (KCs) and monocyte-derived macrophages; high phenotypic and functional heterogeneity and plasticity	Mainly resident KCs; maintain immune tolerance and gut barrier	KCs depleted; bone marrow monocytes recruited and activated	Shift toward pro-fibrotic macrophage phenotypes; promote inflammation and HSC activation	Phenotypic switch to restorative macrophages; promote matrix degradation and fibrosis resolution	[3]
Neutrophils	Innate immune cells; mediate inflammation; short-lived	Low abundance; limited activity	Rapidly recruited; amplify hepatic inflammation	Transient infiltration; limited direct fibrogenic role	May contribute to matrix remodeling and tissue resolution	[3]
Dendritic cells	Antigen-presenting cells; link innate and adaptive immunity	Steady-state antigen sampling; maintain tolerance	Increased activation and antigen presentation	Expanded; role context-dependent and potentially pro- or anti-fibrotic	Possibly involved in restoring immune balance; role remains unclear	[3]
Mast cells	Rare innate immune cells; secrete histamine, cytokines, and growth factors	Sparse population; minimal activity	Minimal involvement	Release profibrotic mediators (e.g., TGF-β, histamine); promote fibrosis	Maintain profibrotic signaling; role in regression remains unclear	[3]
B cells	Adaptive immune cells; produce antibodies and modulate T cell responses	Present in low numbers	Activation and recruitment	Accumulate in fibrotic liver; role remains unclear	Potential immunomodulatory role; unclear	[3]
T_H cells	Conventional T cells CD4$^+$ T helper cells; regulate immune responses through cytokine secretion	Maintain immune balance	Subtype-dependent activation	T_H 1: (IL−12, IFNγ): antifibrotic; T_H 2: (IL−4, IL−13): profibrogenic; T_H 17: (IL−17, IL−22): profibrogenic, IL−22 may be protective	Function depends on cytokine profile shift	[3]
T_{reg} cells	Regulatory T cells; suppress immune activation and maintain tolerance	Support immune tolerance	Recruitment	Inhibit fibrogenesis via IL−10; anti-inflammatory	May support resolution through immune suppression	[3]
CD8$^+$ T cells	Cytotoxic T lymphocytes; eliminate infected or damaged cells	Immunosurveillance	Activated	Contradictory roles: cytotoxic to HSCs (antifibrotic) or promote injury and inflammation (profibrotic)	Context-dependent; not fully understood	[3]
NKT cells	Unconventional T cells bridging innate and adaptive immunity	Surveillance role	Activated	Dual role: IL−4/IL−13 – profibrotic; IFN-γ – antifibrotic via killing of activated HSCs	Context-dependent protective role	[3]
MAIT cells	Innate-like T cells recognizing microbial metabolites via MR1	Enriched in liver	Activated	Role under investigation; may participate in immune regulation and inflammation	Unclear; function still evolving	[3]
γδT cells	Unconventional T cells; recognize stress ligands without MHC	Immune surveillance	Activated	Accumulate in fibrotic livers; precise role remains unclear	Involvement unclear; possibly context-specific	[3]

(*continued on next page*)

Table 1 (*continued*)

Cell Type	Description	Liver homeostasis	Acute liver injury	Chronic liver fibrosis	Fibrosis regression	Ref
NK cells	Innate lymphoid cells	Kill activated cells	Activated	Eliminate activated HSCs; protective effect may vary by subtype or disease stage	May aid resolution by targeting fibrogenic cells	[3]
HSCs	Main effector cells in liver fibrosis; reside in the space of Disse; store vitamin A in lipid droplets	Quiescent; contain retinoid-rich lipid droplets	Activated	Transdifferentiate into myofibroblasts: ↑α-SMA, ↑Collagen I, ↑TIMP, ↑inflammatory mediators; vitamin A loss	Inactivation, apoptosis, or senescence	[3,36]
Portal fibroblasts	Mesenchymal cells near portal veins; contribute to structural support and ECM production	Small quiescent population; structural support	Activated in cholestatic injury	Source of myofibroblasts in biliary/portal fibrosis	Possible reversion or clearance	[3,36]
Myofibroblasts	Activated fibrogenic cells mainly derived from HSCs and portal fibroblasts; major ECM-producing cells	Absent	Emerge from HSC/portal fibroblast activation	Major source of ECM; secrete collagen and fibrosis-related molecules	Apoptosis or reversion to quiescent phenotype	[3,24,36]

exhibit intrinsic self-renewal capacity and phenotypic stability during cellular turnover[37,38]. Immune cells are distributed throughout the hepatic microenvironment, with a predominant accumulation in periportal regions[39]. Among them, liver-resident Kupffer cells form a critical component of the hepatic mononuclear phagocyte system, tasked with the clearance of apoptotic debris and gut-derived microbial products, thereby contributing to immune surveillance and the maintenance of hepatic immune tolerance[3,40]. HSCs, residing in the space of Disse, remain quiescent under steady-state conditions and are characterized by the presence of retinoid-rich lipid droplets, which might play a role in preserving their quiescent phenotype[24,41]. LSECs, distinguished by their fenestrated morphology and absence of a basement membrane, are fully differentiated and play a key regulatory role in maintaining hepatic homeostasis[42]. Specifically, LSECs modulate hepatocyte proliferation, govern the spatial distribution of Kupffer cells, and actively contribute to the maintenance of HSC quiescence through paracrine signaling mechanisms[43].

2.2.2. *Liver fibrosis*

Liver injury represents the initiating event in the pathogenesis of hepatic fibrosis and can be broadly categorized into two types: hepatotoxic injury—commonly resulting from viral infections, alcohol abuse, or metabolic dysfunction—and cholestatic injury, which arises from impaired bile flow[36].

During acute liver injury, hepatocytes and cholangiocytes exhibit a proliferative response aimed at replenishing lost or damaged cells and restoring tissue homeostasis[37,38]. In parallel, injured or dying hepatic cells release damage-associated molecular patterns (DAMPs), while microbial products from the gut contribute pathogen-associated molecular patterns (PAMPs)[3]. These danger signals are sensed by resident and infiltrating immune cells, thereby triggering a robust inflammatory cascade[44]. Activated immune cells, including Kupffer cells, infiltrating monocytes, and neutrophils, produce pro-fibrogenic mediators such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), which act on HSCs, driving their activation and promoting ECM deposition[3,13,45]. Initially, ECM accumulation may serve as a reparative response to stabilize the damaged parenchyma; however, excessive or unresolved ECM production ultimately leads to scar formation and fibrosis[46]. Notably, damaged hepatocytes themselves can also secrete TGF-β, further promoting HSC activation[47].

In addition, LSECs undergo capillarization in response to injury, characterized by the loss of fenestrae and the acquisition of a basement membrane[42]. This phenotypic transition compromises their ability to maintain HSC quiescence, partly due to reduced production of NO and diminished secretion of chemokines such as CXCL9 and CXCL10, which are known to restrain HSC activation[43,48]. Furthermore, decreased expression of vascular endothelial growth factor A (VEGF-A) by capillarized LSECs disrupts the VEGF–NO axis, exacerbating sinusoidal dysfunction[43,48]. As a result, capillarized LSECs not only promote HSC activation but also impair hepatocyte proliferation and facilitate immune cell infiltration, thereby perpetuating a vicious cycle of chronic inflammation and fibrogenesis.

If the underlying etiological factors causing liver injury are not effectively eliminated, hepatic damage may persist over several years, leading to chronic liver injury. This chronic insult significantly accelerates disease progression and complicates therapeutic intervention. During chronic liver injury, hepatocytes are progressively lost due to apoptosis and senescence, resulting in severely impaired regenerative capacity. In this context, cholangiocytes may attempt to compensate by giving rise to liver progenitor cells (LPCs), which can differentiate into hepatocytes[38]. However, this alternative regenerative pathway is often inefficient and constrained by the fibrotic and inflammatory microenvironment.

A critical feature of chronic liver injury is the bidirectional interplay between immune cells and HSCs. On one hand, activated immune cells continuously secrete pro-inflammatory and pro-fibrogenic cytokines, such as TGF-β and IL-1β, thereby sustaining HSC activation[3]. On the other hand, activated HSCs differentiate into myofibroblasts and, in turn, secrete inflammatory mediators and chemokines—including CCL2 and IL-6—that further recruit and activate immune cells. This mutual amplification forms a chronic inflammatory-fibrotic loop, exacerbating tissue damage[3]. Concomitantly, there is excessive accumulation of ECM, accompanied by qualitative changes such as increased stiffness [46]. The altered mechanical properties of the ECM disrupt hepatic architecture, impair hepatocyte function, and promote irreversible tissue remodeling[46]. As fibrosis progresses, normal parenchymal tissue is gradually replaced by scar tissue. In advanced stages, this culminates in liver cirrhosis, characterized by regenerative nodules, vascular remodeling, and architectural distortion. Eventually, end-stage complications such as liver failure or hepatocellular carcinoma may arise.

2.2.3. *Liver regression*

During the regression phase of liver fibrosis, the primary therapeutic goals are to prevent hepatocyte apoptosis and to induce senescence, apoptosis, or inactivation of HSCs and myofibroblasts. Notably, the inactivation of HSCs does not represent a complete reversion to their quiescent phenotype, but rather a transition into a "quiescence-like" state that enables them to evade apoptosis while retaining the capacity to rapidly respond upon re-exposure to fibrogenic stimuli[41]. Although immune cells are widely recognized for their pro-inflammatory and pro-fibrotic roles in chronic liver injury, their functions in the context of liver fibrosis are increasingly understood to be heterogeneous and context-dependent. Recent single-cell transcriptomic analyses have revealed remarkable diversity and plasticity among hepatic immune

populations[49–51]. Depending on the immune cell type, activation state, and disease context, immune cells may exert either pro-fibrotic or anti-fibrotic effects. Emerging evidence suggests that immune cells can actively contribute to fibrosis resolution. For instance, certain immune cell subsets can promote the apoptosis of activated HSCs. Neutrophils facilitate the phenotypic shift of macrophages toward a restorative phenotype[52]. This state is characterized by increased anti-inflammatory cytokine production and reduced pro-inflammatory activity. Moreover, neutrophils may directly promote matrix degradation and vascular regeneration. Among lymphocytes, γδT cells and tissue-resident memory $CD8^+$ T cells can induce apoptosis of activated HSCs via the Fas–FasL pathway[3]. In addition, NKT cells may contribute to fibrosis resolution by inducing apoptosis of activated HSCs through cytokine secretion, such as interferon-γ (IFN-γ), or via direct cytotoxic mechanisms[3]. Similarly, natural killer (NK) cells can mediate cytotoxicity against HSCs through NKG2D-dependent recognition[3]. These findings underscore the dualistic and dynamic roles of immune cells in both the progression and resolution of liver fibrosis.

Recent technological advancements have challenged the traditional categorization of liver fibrosis progression into discrete stages—liver injury, inflammation, fibrogenesis, and either regression or progression to advanced liver diseases—highlighting its limitations in clinical applications. In reality, these processes, along with their associated pathogenic mediators and cellular interactions, form a complex, dynamic network rather than a linear sequence. The development of multicellular in vitro models and sophisticated mouse models has provided more accurate representations of human pathological mechanisms [8–10]. Additionally, the rapid expansion of omics technologies, including single-cell transcriptomics, proteomics, lipidomics, and spatial transcriptomics, has unveiled the heterogeneity and dynamic behavior of cellular populations[7,11]. These breakthroughs have significantly deepened our understanding of the pathophysiological mechanisms underlying liver fibrosis and have greatly enhanced the translation of these insights into clinical applications.

2.3. Diagnosis and treatment

Several studies have suggested that hepatic fibrosis is reversible, and under certain conditions—such as antiviral therapy—liver cirrhosis may also be reversible[53]. However, once liver fibrosis progresses to its later stages, it becomes irreversible. Therefore, early diagnosis and timely intervention hold promise for the potential reversal of liver fibrosis. The challenge, however, lies in the fact that diagnosis methods for liver fibrosis are still in the developmental stage, while its incidence continues to rise annually without the availability of effective therapies. Liver biopsy has long been considered the "gold standard" for liver disease assessment, but it has notable limitations, including sampling errors, observer variability, and an inability to reflect the dynamic balance of matrix production and degradation[4]. Consequently, there is an urgent need to develop more accurate and non-invasive diagnostic strategies. Recent research has focused on biomarker-based approaches, elastography imaging, and large-scale population screening to improve early detection of liver fibrosis.

Transient elastography is a well-established ultrasound-based elastography technique for the noninvasive diagnosis and staging of liver fibrosis in patients with MASLD. One of its key advantages is that it can typically be completed in a relatively short period (usually within five minutes), and it demonstrates excellent intraobserver and interobserver reliability. However, there are some limitations. For instance, the procedure may be less effective in obese patients, and scan results can be inconsistent when performed by inexperienced operators. Most importantly, its diagnostic accuracy is limited in detecting early-stage liver fibrosis[54]. A systematic review incorporating 14 studies investigated the application of VCTE as a non-invasive method in patients with autoimmune liver diseases. The findings demonstrated that VCTE exhibits high diagnostic accuracy for fibrosis staging and serves as a valuable tool for assessing and monitoring fibrosis progression in these chronic conditions[55]. Another study demonstrated that **Fi**brosis-4 (FIB-4) index exhibits moderate diagnostic accuracy in identifying and excluding advanced fibrosis in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease[56]. As research on non-invasive imaging biomarkers advances, it is expected that the integration of artificial intelligence (AI) technology will improve the accuracy of existing diagnostic equipment and maximize its efficiency in the future[54].

Although several noninvasive methods and referral pathways exist for the early detection of liver fibrosis, effective screening programs must ensure not only accurate diagnosis but also cost-effectiveness and demonstrable clinical benefits, such as reduced liver-related mortality. These benefits require validation through randomized controlled trials. Future randomized screening trials should assess not only the effectiveness of screening tests but also the impact of interventions designed to halt disease progression in individuals identified through screening [57]. In the early stages of liver fibrosis, eliminating pathogenic factors and adopting lifestyle modifications may alleviate or even reverse the condition. However, in advanced stages, liver transplantation often remains the sole viable treatment option. Despite its efficacy, clinical application is severely restricted by donor shortages, immune rejection, and excessive medical costs. Consequently, there is an urgent need to develop safe and effective antifibrotic therapies to mitigate the global health burden posed by liver fibrosis.

3. Endoplasmic reticulum stress (ER stress)

The liver depends on an extensive endoplasmic reticulum (ER) network to facilitate efficient protein folding and respond to various internal and external signals. These signals play a crucial role in mediating metabolic changes in the liver. Several factors, including the accumulation of unfolded or misfolded proteins and lipid overload, can trigger ER stress, which has been shown to drive the progression of liver fibrosis. Notably, key ER stress markers such as GRP78 and C/EBP homologous protein (CHOP) are highly expressed in both animal models and patients with advanced liver fibrosis. Moreover, ER stress is critically involved in hepatocytes and hepatic stellate cells (HSCs), two cell types with inherently high ER expression, reflecting the liver's intensive protein synthesis and secretion demands. In hepatocytes, the ER is primarily responsible for synthesizing and secreting proteins essential for metabolism, detoxification, and bile production. In HSCs, ER stress contributes to their activation and transformation into myofibroblasts, a process involving extensive ER remodeling. Additionally, in Kupffer cells (KCs), ER stress may amplify inflammatory signaling, further exacerbating liver injury and fibrosis.

The ER plays a crucial role in maintaining cellular homeostasis through its quality control system, which ensures proper protein folding and facilitates the degradation of misfolded or aggregated proteins[15]. The UPR is a central mechanism through which the ER preserves its functionality. The UPR is activated in response to the accumulation of unfolded or misfolded proteins within the ER lumen, triggering three primary signaling pathways: inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6). These pathways work synergistically to reduce the burden of unfolded proteins, enhance protein-folding capacity, and restore ER homeostasis. IRE1 activates X-box binding protein 1 (XBP1), which upregulates the expression of molecular chaperones and ERAD components. PERK phosphorylates eukaryotic initiation factor 2α (eIF2α), leading to translational attenuation, thereby allowing the ER to focus on protein refolding and stress resolution. ATF6 translocates to the Golgi apparatus, where it undergoes proteolytic activation before migrating to the nucleus to induce the expression of genes involved in protein quality control. Collectively, these signaling cascades ensure ER stability and cellular proteostasis under stress conditions. However, when ER stress persists and the UPR becomes overwhelmed, it can lead to cellular dysfunction, apoptosis, and the progression of liver diseases such as

fibrosis, cirrhosis, and HCC. Chronic ER stress is a key contributor to the activation of HSCs and the accumulation of ECM components, driving liver fibrosis. Moreover, prolonged ER stress disrupts cellular metabolism and enhances inflammatory signaling, thereby exacerbating liver injury. Given its critical role in liver pathophysiology, targeting ER stress and UPR signaling pathways represents a promising therapeutic approach for mitigating liver fibrosis and other chronic liver diseases.

3.1. The ER as a quality control system

The ER is a single-membrane-enclosed organelle unique to eukaryotic cells, serving as a quality control system that regulates several well-coordinated cellular processes, including protein maturation, lipid biosynthesis, and calcium storage, thereby maintaining cellular homeostasis. Structurally, the ER consists of the double-layered nuclear envelope and the peripheral ER, which is composed of high-density, interconnected rough ER (rER) sheets and reticulated smooth ER (sER) tubules[58]. The relative abundance of rER and sER varies depending on cell type and functional demands[59]. Morphologically, rER is distinguished by the presence of ribosomes on its surface, whereas sER lacks ribosomes[58]. This structural specialization reflects their specialized functions, with the ER's architecture dynamically adapting to cellular needs. The sER serves as the primary site for lipid synthesis and is pivotal in Ca^{2+} signaling and transportation between organelles[60]. In contrast, the rER is mainly responsible for the synthesis of secretory and membrane proteins. Nearly one-third of proteins in eukaryotic cells are synthesized, modified, and properly folded within the ER, aided by protein-folding enzymes and molecular chaperones. These proteins are then trafficked to their final destinations or secreted[61]. The ER plays a crucial role in this process by functioning as a quality control system, ensuring the generation of correctly folded proteins, which is essential for cell survival and function[15].

3.2. ER stress response

When the ER quality control system is disrupted, ER stress is triggered, characterized by the accumulation of unfolded or misfolded proteins in the ER lumen. This can result from a sudden increase in the demand for secreted or membrane proteins, as well as various cellular stressors, including redox imbalance, Ca^{2+} homeostasis disruptions, protein glycosylation errors, or genetic mutations. In response to ER stress, cells activate a series of defense mechanisms, collectively termed the ER stress response, to mitigate cellular stress and promote survival. This response comprises three primary pathways: ERAD, the UPR, and autophagy, all of which are critical for maintaining protein homeostasis. Specifically, ERAD facilitates the degradation of misfolded proteins, the

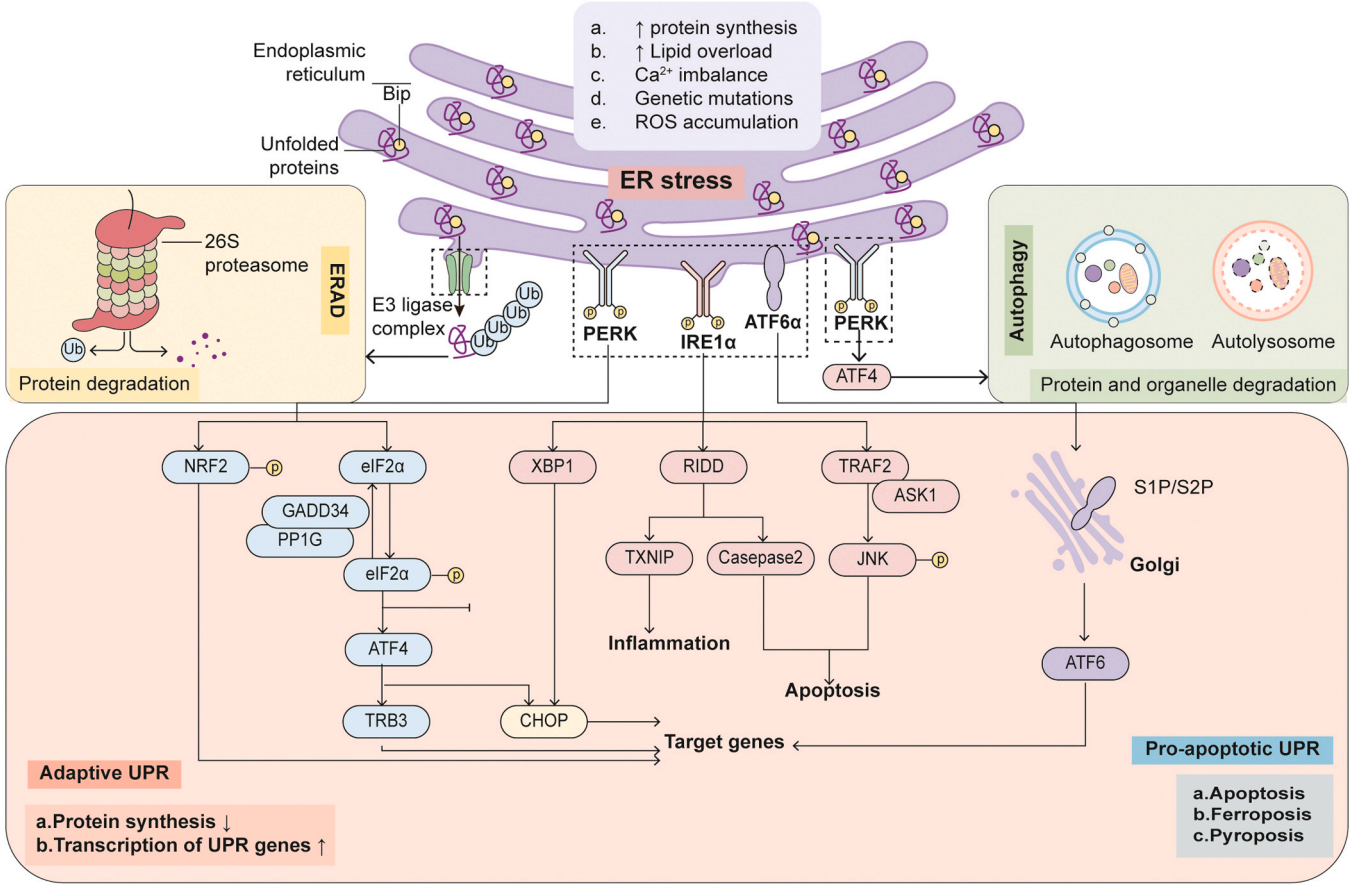


Fig. 2. ER response in liver fibrosis. Endoplasmic reticulum (ER) stress plays a critical role in liver fibrosis, triggered by multiple factors including protein synthesis overload, lipid accumulation, calcium imbalance, genetic mutations, and reactive oxygen species (ROS) accumulation. These stressors lead to the accumulation of unfolded proteins in the ER, activating a series of adaptive and pro-apoptotic unfolded protein response (UPR) pathways. The adaptive UPR pathway, involving key proteins like PERK, IRE1α, ATF6, and ATF4, aims to restore cellular homeostasis through the transcription of stress-responsive genes and the regulation of protein degradation mechanisms. The pro-apoptotic UPR pathway, triggered by ATF6 and other pro-apoptotic molecules, induces inflammation and apoptosis, contributing to liver injury. In addition, ER stress can modulate autophagic processes, including autophagosome formation and protein degradation. The balance between adaptive and pro-apoptotic responses dictates the progression of liver fibrosis, influencing tissue remodeling, inflammation, and cell survival. Abbreviations: ATF, activating transcription factor; ATF4, activating transcription factor 4; CHOP, C/EBP homologous protein; ER, endoplasmic reticulum; IRE1α, inositol-requiring enzyme 1 alpha; NRF2, nuclear factor erythroid 2-related factor 2; PERK, protein kinase RNA-like ER kinase; ROS, reactive oxygen species; TRB3, tribbles homolog 3; UPR, unfolded protein response; XBP1, X-box binding protein 1.

UPR alleviates the burden of unfolded proteins while enhancing protein-folding capacity, and autophagy contributes to the clearance of misfolded proteins and recycling of cellular components. However, when ER stress becomes chronic or excessive, it can initiate inflammatory responses and activate cell death pathways, ultimately leading to cellular dysfunction and disease progression. Fig. 2 illustrates the ER response, while Table 2 summarizes the key molecules involved in this process.

3.3. ERAD

The ERAD pathway serves as the primary defense mechanism of the ER, responsible for identifying and removing defective, unfolded, or misfolded proteins, as well as by-products of protein synthesis, from the ER lumen or membrane into the cytosol for subsequent degradation. Recent studies suggest that ERAD consists of a series of independent processes, with ER-membrane-embedded ubiquitin ligases (ER-E3s) acting as a central hub in this pathwayb[62–64]. Initially, recognition factors detect atypical features of damaged substrates, guiding them toward E3 ligases for specific identification. Following recognition, substrates are transported into the cytoplasm via two main routes: soluble proteins undergo retrotranslocation via the HRD1 E3 complex, whereas integral membrane proteins are dislocated through various ERAD pathways. Next, the membrane-associated ubiquitylation machinery modifies these substrates by adding ubiquitin chains, a step closely linked to the subsequent process, in which the ubiquitin-dependent enzyme VCP (or Cdc48) extracts polyubiquitylated substrates from the ER. After extraction, the ubiquitin signal is refined by deubiquitylating and ubiquitin chain-elongating enzymes, ensuring substrates are properly processed for degradation. Finally, these remodeled substrates are delivered to the 26S proteasome for proteolytic degradation. Beyond its role in protein quality control, ERAD also participates in other biological processes, including membrane fluidity, ferroptosis, iron metabolism, innate immune signaling, and sleep, which will not be elaborated upon here[62]. While ERAD functions as the first line of defense in maintaining ER protein homeostasis and mitigating protein toxicity caused by ER stress, its activation has also been implicated in the pathogenesis of certain diseases. Recent studies have primarily focused on the role of ERAD in hepatic lipid accumulation, whereas its involvement in liver fibrosis remains relatively underexplored[65–70].

Table 2
ER stress response.

ER stress Response	Key Molecules	Functions	Ref
ERAD	UPS; E3-ligase; 26S proteasome	Degradation of detective or unwanted proteins	[62]
UPR	IRE1A-PERK-ATF6	Decrease the load of unfolded protein Increase the protein folding capacity	[35]
UPR-IRE1A	XBP1-RIDD-TRAF2-JNK	Protein trafficking; Protein folding; Degradation	[211]
UPR-PERK	eIF2α-ATF4	Amino acid metabolism; Oxidative stress resistance; Autophagy	[211]
UPR-ATF6	ATF6-S1P-S2P	Protein folding; ER degradation; ER biogenesis	[211]
Autophagy	Autosome; ATG7	Recycling of misfolded proteins and cellular materials	[35]
Apoptosis	CHOP; JNK1	Exacerbates liver injury	[35]

3.4. UPR

When the ERAD pathway fails to restore ER homeostasis, eukaryotic cells activate the ER-nucleus signaling system, referred to as the "unfolded protein response" (UPR), to either resolve ER stress or initiate cell death. The UPR pathway is activated by three key ER transmembrane proteins, commonly referred to as UPR sensors: PERK, IRE1α, and ATF6. Under normal conditions, these UPR sensors remain inactive due to their association with the major ER-resident chaperone protein BiP (immunoglobulin heavy chain-binding protein, also known as the 78 kDa glucose-regulated protein, GRP78). BiP, a member of the heat shock protein 70 (Hsp70) family, contains an N-terminal signal peptide for ER localization and a C-terminal KDEL (Lys-Asp-Glu-Leu) motif, which facilitates its retrieval from the Golgi apparatus and retention in the ER, ensuring its critical role in regulating the UPR and maintaining ER homeostasis. Upon ER stress, BiP preferentially binds to unfolded or misfolded proteins accumulating in the ER lumen, causing it to dissociate from the UPR sensors. This dissociation allows the sensors to oligomerize and become active, initiating the UPR—a widely recognized activation pathway. Some studies suggest that unfolded proteins can also directly bind to the luminal domains of the sensors, triggering their activation. Additionally, under lipotoxic conditions, IRE1α and PERK can be activated through their transmembrane domains.

The first branch of UPR involves IRE1, which is highly conserved in eukaryotic cells[71,72]. The mammalian genome encodes two isoforms of IRE1: IRE1α (encoded by *ERN1*) and IRE1β (encoded by *ERN2*), which exhibit distinct expression patterns. IRE1α is ubiquitously expressed, whereas IRE1β is specifically expressed in intestinal epithelial cells. Furthermore, due to differences in their RNase domains and substrate specificities, they also exhibit distinct functions[73,74]. In this context, we primarily focus on IRE1α, which contains both a kinase and an endoribonuclease cytosolic domain. IRE1α primarily regulates two key pathways: the XBP1 pathway and the RIDD (IRE1α-dependent regulated IRE1 decay) pathway. Additionally, it also participates in the JNK signaling pathway. In the following sections, we will provide a detailed overview of the signaling mechanisms mediated by IRE1α, with a particular focus on its roles in the XBP1 and RIDD pathways, as well as its involvement in the JNK signaling cascade. During ER stress, IRE1α is activated through autophosphorylation, which in turn activates its cytosolic ribonuclease (RNase) domain[75]. This activation catalyzes the splicing of XBP1 mRNA, removing a 26-base intron to generate a shorter XBP1 mRNA. The spliced XBP1 mRNA is then ligated into its active form by the RtcB RNA ligase[76]. The resulting active XBP1s protein is translocated to the nucleus, where it binds to DNA and transactivates a set of UPR-related genes. These include genes involved in the ERAD pathway, ER chaperones, and key enzymes involved in lipid biosynthesis[77,78]. Independent of XBP1, IRE1 degrades non-essential mRNAs and microRNAs through the RIDD mechanism[79,80], with these mRNAs exhibiting a stem-loop recognition motif similar to that of XBP1[81]. This mechanism plays a critical role in regulating cellular survival and death and is particularly significant in hepatic metabolic dysfunction. Both XBP1 and RIDD contribute to alleviating ER stress, but as the stress intensity increases, activation of XBP1 tends to promote survival, while RIDD, if the stress remains unresolved, may exacerbate ER stress and ultimately lead to cell death[72]. We will discuss its application in hepatic metabolic dysfunction in the following sections.

PERK is the second branch of the UPR, encoded by *EIF2AK3*, with its functional domain being a cytosolic kinase domain. Upon dissociation from BiP, PERK forms homodimers and undergoes autophosphorylation, which activates its kinase function, leading to the phosphorylation of its main substrate, eukaryotic translation initiation factor 2α (eIF2α)[75]. This phosphorylation is crucial for PERK signaling. The phosphorylation of eIF2α inhibits the assembly of the 80S ribosome, thereby broadly suppressing translation and reducing the influx of new proteins into the ER[82]. However, this translation inhibition selectively promotes the translation of certain mRNAs with upstream open reading frames

(uORFs), such as the mRNA encoding activating transcription factor 4 (ATF4)[83]. The resulting ATF4 is then translocated to the nucleus, where it regulates the expression of genes involved in amino acid metabolism, transport, and apoptosis, such as tribbles homolog 3 (TRB3) and CHOP, ultimately influencing cell survival or death[84]. Under stress conditions, PERK plays a critical role in balancing cell survival and apoptosis by regulating the expression of these genes, and it is closely associated with the pathogenesis of liver diseases[85,86].

The third branch of the UPR, ATF6, consists of two homologs with distinct transcriptional activation domains: ATF6α and ATF6β. Studies indicate that ATF6β acts as an inhibitory factor, modulating the duration and intensity of ATF6α-mediated gene regulation[87]. In the ER, ATF6 is synthesized as an inactive precursor, with its Golgi localization signals masked by BiP binding[88]. Upon ER stress, ATF6 dissociates from BiP, exposing the Golgi localization signals and translocating to the cis-Golgi, where it is cleaved by site-1 protease (S1P) and site-2 protease (S2P), generating the active form, ATF6p50[89,90]. These proteases also play a role in regulating liver-specific lipid homeostasis. The activated ATF6p50 then translocates to the nucleus, inducing the expression of genes encoding UPR components and ER chaperones such as BiP, CHOP, endoplasmin, and XBP1[91]. Additionally, ATF6p50 can form heterodimers with XBP1, enhancing the expression of ERAD genes[89].

Adaptive UPR is triggered by ER stress, resulting in the activation of its three major branches. These branches facilitate autophagy, mitigate the accumulation of ROS, and inhibit apoptosis, thereby alleviating ER stress and preventing the progression of liver diseases. In contrast, maladaptive UPR occurs when ER stress becomes excessive, leading to the dysregulated overactivation of the same three branches. This aberrant activation promotes excessive autophagy, along with the induction of inflammation and apoptosis, ultimately culminating in cell death and exacerbating the progression of liver diseases[16].

3.5. Autophagy

Autophagy is an intracellular lysosomal degradative pathway considered a dynamic recycling system that links catabolic and anabolic processes to maintain cellular homeostasis[92,93]. The degradation products from autophagy are used for new protein synthesis, energy production, and gluconeogenesis. Autophagy is triggered by starvation or internal and external cellular stresses. It relies on a set of conserved autophagy-related proteins (ATGs), such as light chain 3 (LC3) and the autophagic substrate p62/Sequestosome-1 (p62/SQSTM1), which activate specific mechanisms to initiate the autophagic process[94,95]. Recent studies have identified three major ways in which autophagy regulates metabolism: nutrient regeneration, organelle quality control, and signaling protein regulation. There are three main types of autophagy: microautophagy, macroautophagy, and chaperone-mediated autophagy[93]. Microautophagy mainly involves the sequestration of cytoplasmic components or vesicles into endosomes or lysosomes and is particularly important in cells under amino acid starvation. Macroautophagy and chaperone-mediated autophagy are the predominant forms in hepatocytes. Macroautophagy relies on the formation of an autophagosome, a spherical vesicle that engulfs cytoplasmic components before fusing with lysosomes for degradation. Chaperone-mediated autophagy is more selective, recognizing specific proteins that are transported to lysosomal receptors for degradation. In the ER, autophagy is responsible for delivering damaged organelles, unfolded proteins, and other components to lysosomes for degradation. Moreover, autophagy plays a crucial role in the liver, a key organ in regulating systemic energy metabolism. It is involved in lipid metabolism, inflammation, and fibrosis in the liver. In hepatocytes, autophagy helps to remove lipid droplets[96], while in hepatic stellate cells, it provides energy for their activation by degrading lipid droplets, and also suppresses the production of pro-inflammatory cytokines[97].

3.6. Inflammatory and apoptosis

When ER stress becomes insurmountable and the ER can no longer restore its function, cell death pathways are activated, often accompanied by inflammatory responses. This process involves both apoptosis and inflammation, with key contributions from UPR sensors, redox balance, and calcium homeostasis. Specifically, the PERK-CHOP pathway and the IRE1-JNK1-BAX signaling cascade are triggered, leading to programmed cell death and liver fibrosis[16,22,23,98].

4. Chronic ER stress in liver fibrosis

ER stress plays a dual role in cellular homeostasis, initially activating adaptive responses to restore protein-folding capacity and maintain cellular function. However, when ER stress becomes prolonged and exceeds the cell's compensatory mechanisms, it leads to detrimental effects. Accumulating evidence suggests that chronic ER stress contributes to hepatic fibrogenesis by inducing hepatocyte dysfunction, exacerbating inflammatory and profibrotic signaling pathways, and promoting HSC activation. Elucidating the mechanisms linking sustained ER stress to liver fibrosis may uncover novel therapeutic targets for intervention.

4.1. Chronic ER stress in hepatocyte

Hepatocytes are enriched in the ER, which provides essential enzymes and a hydrophobic environment for lipid synthesis. In hepatocytes, ER stress and lipid accumulation establish a vicious cycle[35]. ER stress not only results from lipid accumulation but also acts as a driving force that exacerbates it. This persistent feedback loop prevents the resolution of initial ER stress, leading to the continuous activation of new ER stress signals and ultimately culminating in chronic ER stress. The sustained ER stress response contributes to oxidative stress, inflammatory signaling, and cell death, thereby accelerating the progression of liver diseases. This section will focus on the relationship between hepatocytes and chronic ER stress, particularly in the context of lipid overload, liver injury, and cell death, and further explore their contribution to liver fibrosis. Fig. 3 illustrates the role of ER stress in hepatocytes.

4.1.1. The vicious cycle of lipid accumulation and ER stress

Lipids are essential and multifunctional metabolites, comprising fatty acids (FAs), triacylglycerols (TAGs), sphingolipids, cholesterol, and phospholipids[99]. They function as key structural components, particularly in the plasma membrane, serve as energy sources due to their highest energy density, and act as critical signaling mediators involved in the regulation of immune and metabolic homeostasis[100]. Lipogenesis, the process by which carbohydrates and other substrates are converted into FAs and subsequently esterified into TAGs, plays a central role in hepatic energy metabolism[99]. This process is orchestrated by multiple enzymes and is tightly regulated by nutrient status and metabolic hormones, such as glucagon, glucocorticoids and insulin [99]. A plethora of signaling pathways is implicated in the modulation of lipogenesis, notably the insulin/PI3K-AKT-mTOR axis[101], AMP-activated protein kinase (AMPK)[102], and transcription factors such as sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate response element-binding protein (ChREBP). Under pathological conditions, dysregulation of these pathways leads to excessive lipid accumulation and metabolic stress in hepatocytes. Surplus FAs are stored as TAGs within lipid droplets (LDs), which triggers lipotoxicity, a condition that impairs cellular function induces cell death [103–105]. In the liver, lipotoxicity contributes to hepatocyte metabolic dysregulation and plays a pivotal role in the progression of liver diseases. Mechanistically, it activates death receptor-mediated signaling pathways, disrupts organelle homeostasis, and induces aberrant stress response gene expression[106]. Among these mechanisms, ER stress

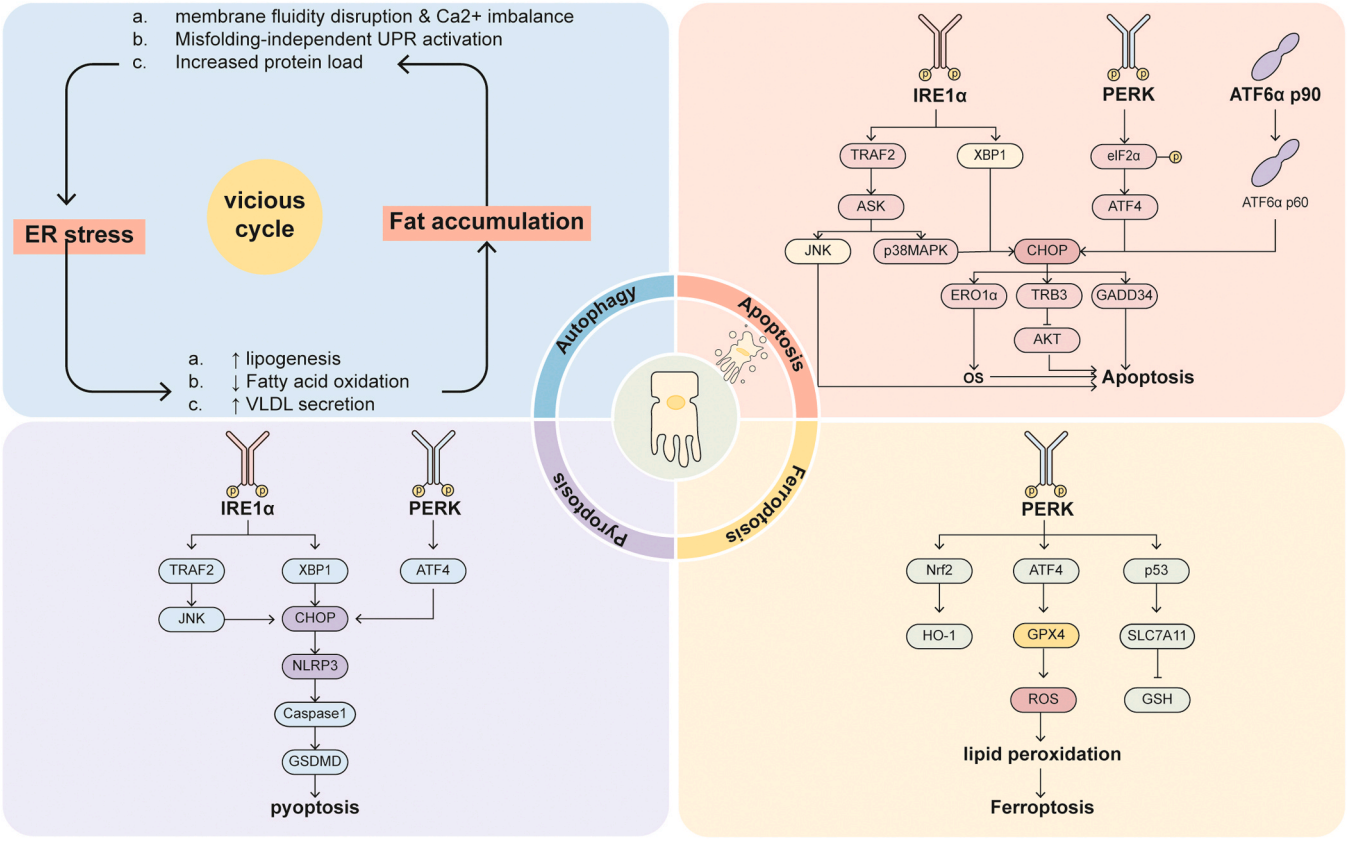


Fig. 3. Chronic ER stress in hepatocytes. Chronic endoplasmic reticulum (ER) stress in hepatocytes contributes to liver dysfunction through a self-perpetuating cycle involving multiple cellular processes. Key stressors—including membrane fluidity disruption, calcium imbalance, and misfolding-independent unfolded protein response (UPR) activation—increase protein load, triggering sustained ER stress. This process promotes fat accumulation in hepatocytes, exacerbating ER stress and fostering liver disease progression. The UPR, mediated by IRE1α, PERK, and ATF6 pathways, plays a pivotal role in this cascade. Chronic activation of these pathways induces apoptosis, autophagy, and ferroptosis, while IRE1α and PERK signaling regulate lipid metabolism, including lipogenesis, fatty acid oxidation, and very-low-density lipoprotein (VLDL) secretion. Additionally, prolonged ER stress drives oxidative stress and lipid peroxidation, contributing to hepatocyte injury and fibrosis. Abbreviations: ATF, activating transcription factor; CHOP, C/EBP homologous protein; ER, endoplasmic reticulum; GSH, glutathione; IRE1α, inositol-requiring enzyme 1 alpha; PERK, protein kinase RNA-like ER kinase; ROS, reactive oxygen species; VLDL, very-low-density lipoprotein.

plays a critical role in mediating the detrimental effects of lipid accumulation. Lipid overload has been shown to trigger ER stress, which in turn exacerbates lipid accumulation, establishing a detrimental feedback loop [35,107]. This section highlights the interplay between lipid accumulation and ER stress, and their roles in liver fibrosis progression.

Lipid-induced ER stress was initially identified in pancreatic β cells, and subsequent studies confirmed that exposure to fatty acids or increased intracellular lipid saturation can activate ER stress[108–110]. Mechanistically, lipid accumulation induces ER stress through two primary pathways.

The first mechanism involves the disruption of membrane fluidity and calcium homeostasis caused by lipid overload. Studies have shown that lipid accumulation increases the phosphatidylcholine (PC) to phosphatidylethanolamine (PE) ratio—two of the most abundant phospholipids in the endoplasmic reticulum (ER) membrane—resulting in reduced membrane fluidity[111–113]. SERCA, a calcium pump residing in the ER membrane, is responsible for pumping Ca^{2+} into the ER lumen, and its activity is highly dependent on the physical properties of the surrounding lipid environment[114]. SERCA2 functions optimally in a highly fluid membrane that is low in cholesterol content [114]. An elevated PC/PE ratio, by decreasing membrane fluidity, may suppress SERCA2 activity[115,116]. Indeed, studies have shown that in obese mice, the expression and/or activity of SERCA2b in hepatocyte ER is significantly reduced, which correlates with decreased ER luminal Ca^{2+} concentration[117]. This suggests that reduced SERCA2b activity compromises ER calcium storage capacity and disrupts calcium homeostasis. Since many ER-resident molecular chaperones are calcium-dependent, this disturbance in calcium homeostasis sensitizes the ER to stress and contributes to the onset of ER stress responses[116].

Second, studies have shown that even when the luminal unfolded protein sensing domains of IRE1 and PERK are deleted, saturated fatty acids (SFAs) can still activate the UPR, indicating that lipid accumulation can induce UPR activation via a mechanism independent of misfolded protein accumulation[35]. Additionally, increased synthesis of proteins associated with very-low-density lipoprotein (VLDL) secretion and lipid droplet formation further exacerbates ER stress, amplifying cellular stress responses and ultimately leading to ER dysfunction[118,119].

ER stress is closely linked to lipid metabolism and contributes to lipid accumulation through multiple mechanisms, including enhanced lipid synthesis, inhibited fatty acid oxidation, and impaired VLDL secretion [35]. Specifically, ER stress activates the SREBP-1c and XBP1 pathways, upregulating lipid synthesis-related genes. Meanwhile, CHOP-mediated suppression of PPARα reduces fatty acid oxidation, leading to decreased lipid consumption. Additionally, impaired IRE1 function disrupts the proper folding of ApoB, thereby inhibiting VLDL secretion and increasing intracellular lipid load. Together, these mechanisms establish ER stress as a critical regulator of lipid accumulation, playing a key role in the progression of MASLD and related disorders. First, ER stress can activate SREBP-1c in the absence of insulin, directly promoting lipid synthesis. Studies have shown that overexpression of the ER chaperone GRP78 suppresses ER stress, thereby reducing SREBP-1c proteolytic

activation and its downstream lipid synthesis gene expression, ultimately improving hepatic steatosis and insulin resistance[120]. This finding suggests that modulating ER stress may offer novel therapeutic strategies for lipid metabolism-related disorders.

Furthermore, ER stress regulates lipid synthesis through the activation of the UPR pathways. The IRE1α pathway generally functions to inhibit lipogenesis and maintain VLDL secretion homeostasis, thereby mitigating hepatic steatosis. However, some studies suggest that IRE1α can also promote de novo lipid synthesis via XBP1 activation. Specifically, XBP1 enhances SREBP-1c activity, indirectly promoting lipid synthesis. One potential mechanism is that XBP1 selectively induces the transcription of FOXA3, which in turn regulates the expression of Per1. Upregulation of Per1 enhances the expression of multiple lipid synthesis genes, including SREBP-1c, thereby facilitating lipid accumulation [121]. On the other hand, in the absence of XBP1, compensatory activation of IRE1 leads to the degradation of lipid metabolism-related cytosolic mRNAs through the regulated RIDD pathway, thereby suppressing lipogenesis[122].

Within the PERK-mediated UPR pathway, ER stress primarily functions to enhance lipid synthesis. PERK deficiency leads to reduced lipid synthesis, while PERK-mediated phosphorylation of eIF2α activates SREBP-1c and SREBP-2, promoting lipid accumulation and exacerbating hepatic steatosis. Overexpression of the eIF2α-specific phosphatase GADD34 or the downstream target ATF4 facilitates sustained eIF2α dephosphorylation, thereby protecting mice from hepatic steatosis. Moreover, certain antipsychotic drugs have been shown to enhance SREBP-1c and SREBP-2 activity via the PERK-eIF2α pathway, further worsening hepatic steatosis. However, knockout of CHOP, a downstream target of PERK, results in increased lipid synthesis, suggesting that CHOP may play a protective role in reducing lipid accumulation and mitigating hepatic steatosis.

The ATF6 pathway inhibits cholesterol synthesis by suppressing SREBP-2 activity through HDAC1. However, loss of ATF6α has been shown to promote lipid accumulation by upregulating SREBP-1c, thereby exacerbating hepatic steatosis. In terms of fatty acid oxidation, activation of IRE1 has been shown to reduce both fatty acid oxidation and lipolysis. CHOP contributes to lipid metabolic dysregulation by suppressing C/EBPα expression, thereby inhibiting fatty acid oxidation and lipoprotein secretion. In contrast, ATF6 promotes fatty acid oxidation by enhancing the expression of CPT1A, MCAD, and FGF21 through the PPARα/PPRE signaling pathway. Studies have demonstrated that Atf6α knockout mice exhibit impaired β-oxidation of fatty acids, leading to hepatic lipid accumulation. Both IRE1 and ATF6 play essential roles in maintaining VLDL secretion and preventing excessive hepatic lipid accumulation, whereas CHOP exerts opposing effects, further exacerbating lipid accumulation and metabolic imbalance.

Overall, the three branches of the UPR activated by ER stress play a crucial role in lipid metabolism regulation, yet their effects are not always consistent. For instance, while the IRE1 pathway generally suppresses hepatic steatosis, its downstream effector XBP1 promotes lipid synthesis. Additionally, IRE1 exhibits pro-inflammatory properties, which may contribute to the progression from MSFLD to MASH. The interplay between the three UPR branches can also lead to opposing effects depending on the pathological context. Under conditions of chronic ER stress, UPR signaling tends to favor disease progression. While most studies have focused on its role in metabolic liver diseases, its specific impact on liver fibrosis remains unclear. It is hypothesized that chronic ER stress may exacerbate hepatocellular injury and inflammation, promoting the transition from MASH to fibrosis. In recent years, lipotoxicity inhibitors have emerged as a promising strategy for alleviating metabolic liver diseases. A natural anti-lipotoxic compound, HN-001, has been identified from the marine fungus Aspergillus sp. C1. HN-001 alleviates palmitic acid (PA)-induced hepatocyte death in a dose- and time-dependent manner. Mechanistically, it inhibits IRE1α-mediated XBP1s splicing and nuclear translocation, thereby reducing lipotoxicity. Furthermore, HN-001 suppresses phospholipase A2 (PLA2) activity and decreases lysophosphatidylcholine (LPC) levels, further mitigating lipotoxicity and inhibiting the pro-apoptotic JNK signaling pathway. Animal studies have demonstrated that HN-001 significantly improves multiple pathological features of MASLD, including hepatic steatosis, liver injury, inflammation, and fibrosis[123].

4.1.2. Regulation of ER Stress-Induced ferroptosis in hepatocyte death

Ferroptosis, a form of iron-dependent programmed cell death, is characterized by the accumulation of lipid peroxides[124]. ER stress can induce ferroptosis by activating pathways associated with lipid peroxidation, thereby exacerbating hepatocyte injury.

4.1.2.1. IRE1-XBP1. Recent studies have highlighted the involvement of the IRE1-XBP1 pathway in upregulating Gα-12, a key mediator of ferroptotic cell death in hepatocytes. The overexpression of Gα-12 promotes ferroptosis through two interrelated signaling cascades, each contributing to lipid peroxidation and cell vulnerability. The first pathway involves the Gα-12/ROCK1/ALOX12 axis, where Gα-12 suppresses ROCK1-mediated miR-15a expression, a known inhibitor of ALOX12[125]. This suppression leads to aberrant activation of ALOX12, which in turn downregulates GPX4, a crucial antioxidant enzyme that protects cells from ferroptosis. The loss of GPX4 activity results in excessive lipid peroxidation, ultimately driving hepatocyte ferroptosis. In a complementary mechanism, the Gα-12/miR-125a/NEMO axis further reinforces ferroptotic signaling. Gα-12 enhances the expression of miR-125a, a microRNA that inhibits NEMO, a positive regulator of GPX4. Given that NEMO promotes GPX4 expression, its suppression leads to further depletion of GPX4, exacerbating ferroptosis[126]. Interestingly, the transcription factor Nrf2 emerges as a protective modulator in this process. As an activator of the IKBKG gene (encoding NEMO), Nrf2 counteracts the Gα-12-induced upregulation of miR-125a, thereby preserving the stability of the NEMO-GPX4 axis[126]. This regulatory balance suggests that the Nrf2-NEMO axis may serve as a critical protective mechanism against ERS-induced ferroptosis in hepatocytes. Collectively, these findings provide novel insights into the role of ER stress in hepatocyte ferroptosis and underscore potential therapeutic strategies targeting the Nrf2-NEMO axis to mitigate liver injury.

4.1.2.2. ATF4. ATF4 is a downstream molecule of the PERK signaling pathway. Its deletion can inhibit hepatic steatosis, but at the same time, it downregulates the expression of SLC7A11 (xCT), thereby enhancing cellular sensitivity to ferroptosis. As a key transcription factor for maintaining oxidative homeostasis and cell survival, ATF4 inhibits ferroptosis by regulating the GSH-GPX4 axis[127]. ATF4 regulates ferroptosis through two main pathways. First, ATF4 can bind to the amino acid response element (AARE) of SLC7A11 (xCT), promoting cysteine uptake across the membrane. Second, ATF4 binds to the cis-regulatory element (CRE) to enhance the transcription of cystathionine γ-lyase (CTH), thereby boosting cysteine biosynthesis. These mechanisms work synergistically to maintain intracellular GSH (glutathione) levels, ensure GPX4 (glutathione peroxidase 4) activity, and ultimately suppress lipid peroxidation and prevent ferroptosis[127]. When ATF4 is inhibited or deleted, the expression of SLC7A11 (xCT) and CTH decreases, leading to reduced GSH synthesis and GPX4 inactivation, which in turn induces lipid peroxidation, disrupts membrane integrity, and accelerates ferroptosis. Studies have shown that overexpression of ATF4 or supplementation with SLC7A11 (xCT) or CTH can effectively mitigate ferroptosis and enhance cell survival[127]. ATF4 also plays a crucial role in maintaining the stability of the GSH-GPX4 axis by regulating SLC7A11 (xCT) and CTH, thereby protecting against ferroptosis. The loss or inhibition of ATF4 disrupts the GSH-GPX4 axis, increasing susceptibility to ferroptosis, which presents a potential therapeutic target for ferroptosis-related diseases[127]. Emerging evidence suggests that ER stress-induced ferroptosis contributes to the pathogenesis of liver

diseases, including MASLD/MASH, liver fibrosis, and HCC. Targeting ER stress and ferroptosis-related pathways may offer novel therapeutic strategies for liver disease intervention.

4.1.3. ER stress in hepatocyte apoptosis and liver fibrosis

Hepatocyte apoptosis is a form of programmed cell death and is considered a key driver of liver inflammation and fibrosis. Recent studies have revealed that ER stress plays a crucial role in regulating hepatocyte apoptosis. ER stress triggers cell death through multiple signaling pathways, among which the IRE1 and PERK pathways are particularly significant. Furthermore, hepatocyte apoptosis not only impairs liver function but also promotes HSC activation via the release of apoptotic bodies, thereby accelerating liver fibrosis.

4.1.3.1. IRE1α. Under chronic ER stress, the IRE1 pathway promotes apoptosis by activating pro-apoptotic and inflammatory proteins, such as CHOP and JNK. IRE1 induces apoptosis via the IRE1-XBP1-CHOP axis and recruits TRAF2, which subsequently activates the ASK1-JNK signaling pathway. JNK phosphorylates and inhibits anti-apoptotic proteins (e.g., BCL-2, BCL-XL, MCL1) while activating pro-apoptotic proteins (e.g., BID, BIM), ultimately leading to cell death. Interestingly, Fortilin can directly bind to the cytoplasmic domain of IRE1α, inhibiting its kinase and RNase activities, thereby attenuating ER stress-induced apoptosis. Studies using cell and animal models have confirmed that Fortilin plays a protective role in the UPR, suggesting its potential as a novel therapeutic target for liver diseases[128].

4.1.3.2. PERK. The PERK pathway mediates apoptosis via the eIF2α-ATF4-CHOP axis. In MASH models, PERK activation increases hepatocyte sensitivity to oxidative stress and lipotoxicity. For example, PA inhibits mitochondrial respiration via the JNK-Sab axis, leading to ROS accumulation and further activation of JNK signaling, ultimately inducing apoptosis. Moreover, PA exacerbates lipotoxic damage through the PERK pathway, promoting hepatocyte death.

4.1.3.3. IRE1α-PERK. There is a crosstalk between the PERK and IRE1 pathways during apoptosis. Research suggests that under prolonged ER stress, PERK activity remains high while IRE1 activity gradually declines, indicating that PERK exerts a stronger pro-apoptotic effect. Additionally, PERK enhances apoptosis by upregulating death receptor 5 (DR5), whereas IRE1 degrades DR5 mRNA via the RIDD pathway, thereby exerting an opposing effect. This temporal regulation highlights that IRE1 primarily functions as a protective mechanism during early ER stress by activating XBP1 splicing, whereas PERK drives apoptosis under sustained stress, ultimately determining cell fate.

4.1.3.4. ATF6. Although ATF6 primarily functions in ER stress adaptation, its prolonged activation can contribute to apoptosis by interacting with CHOP. Additionally, ATF6 interacts with XBP1 to regulate the adaptive UPR response. Under severe and prolonged ER stress, ATF6 may exacerbate hepatocyte apoptosis by upregulating CHOP expression.

4.1.3.5. CD1d-JAK2-STAT3. Beyond classical UPR pathways, the CD1d-JAK2-STAT3 signaling axis also plays a protective role against hepatocyte apoptosis. Studies have shown that CD1d expression is significantly reduced in liver tissues of NASH patients, which correlates with increased hepatocyte apoptosis and exacerbated liver injury. CD1d activates JAK2, which in turn promotes STAT3 phosphorylation, thereby inhibiting pro-apoptotic signaling and protecting hepatocytes from ER stress-induced death. This discovery offers a potential therapeutic strategy for treating NASH and other liver diseases.

Collectively, ER stress-induced hepatocyte apoptosis serves as a key driver of liver fibrosis progression, highlighting potential therapeutic targets for intervention.

4.1.4. ER stress in hepatocyte pyroptosis and liver fibrosis

Pyroptosis is a regulated pro-inflammatory form of cell death, characterized by cell membrane rupture and the excessive release of inflammatory cytokines. This process is critically dependent on the cleavage of gasdermin D (GSDMD) by caspase-1 and caspase-11/4/5, where the N-terminal domain of GSDMD forms membrane pores, ultimately leading to cell death. Studies have demonstrated that the NLRP3 inflammasome plays a pivotal role in the initiation and regulation of pyroptosis and is strongly associated with MASH and hepatic fibrosis. The NLRP3 inflammasome is a multiprotein complex composed of NOD-like receptor (NLR) family proteins, apoptosis-associated speck-like protein (ASC), and pro-caspase-1. Its activation is typically triggered by PAMPs or DAMPs, which stimulate Toll-like receptor (TLR)-mediated inflammatory signaling cascades. This process subsequently activates the NLRP3 inflammasome, leading to caspase-1 cleavage and the maturation of pro-inflammatory cytokines IL-1β and IL-18. Additionally, activated GSDMD forms membrane pores, causing cell swelling, osmotic lysis, and pyroptotic cell death. Under pathological conditions such as MASH and hepatic fibrosis, hepatocyte pyroptosis is markedly elevated. Studies have shown that excessive NLRP3 activation in hepatocytes can trigger caspase-1-dependent pyroptosis, which in turn activates HSCs and promotes fibrosis progression. Furthermore, ER stress has emerged as a key inducer of hepatocyte pyroptosis. Notably, the IRE1 and PERK signaling pathways can activate NLRP3 via the downstream transcription factor CHOP, thereby inducing pyroptosis and exacerbating liver injury and fibrosis.

4.2. Chronic ER stress in hepatic stellate cell

HSCs were first discovered by von Kupffer in 1876, located in the Disse space between hepatocytes and LSECs[129]. HSCs are the primary source of hepatic fibroblasts[5], along with fibroblasts from other sources such as the portal vein and bone marrow. The activation of HSCs, which involves their transformation into proliferative and fibrogenic myofibroblasts, is the core driving force behind liver fibrosis in both experimental and human liver injuries[24]. However, recent studies have revealed that cells derived from other fibroblast sources are also closely associated with the progression of liver fibrosis.

Under normal physiological conditions, HSCs are in a quiescent state, with their most significant feature being the metabolism and storage of retinol in lipid droplets within the cytoplasm[130] [41]. HSCs also participate in the dynamic balance of the ECM. Upon liver injury, quiescent HSCs are stimulated by various external signals, leading to their trans-differentiation and progressive activation. This process can be divided into initiation and expansion phases. In the initiation phase, HSCs are sensitive to damage signals, transitioning into an activated phenotype. In the expansion phase, the activated phenotype is amplified, characterized by increased proliferation, contractility, fibrogenesis, changes in matrix degradation mechanisms, enhanced chemotaxis, and altered inflammatory signaling[41] [131]. Activated HSCs lose their retinol storage capacity, express α-smooth muscle actin (α-SMA), and secrete collagen and matrix-degrading inhibitors. They also release pro-inflammatory cytokines and chemokines, exacerbating the inflammatory response during liver injury. The specific mechanisms of HSC activation have been extensively discussed in several reviews, which describe the roles of intracellular and extracellular signals in HSC activation and explore the mechanisms of HSC regression, including apoptosis, senescence, and inactivation.

Among the numerous mechanisms that influence HSC activation[5], autophagy and ER stress are particularly critical. Fig. 4 depicts the interplay between ER stress and autophagy in HSCs. Autophagy promotes HSC activation by providing energy substrates, while enhanced ER stress is closely related to functional changes in HSCs. Many cellular events and signaling pathways involved in these processes are considered important potential targets for antifibrotic therapy. Of note, ER stress plays a critical role in the activation of HSCs and the progression of

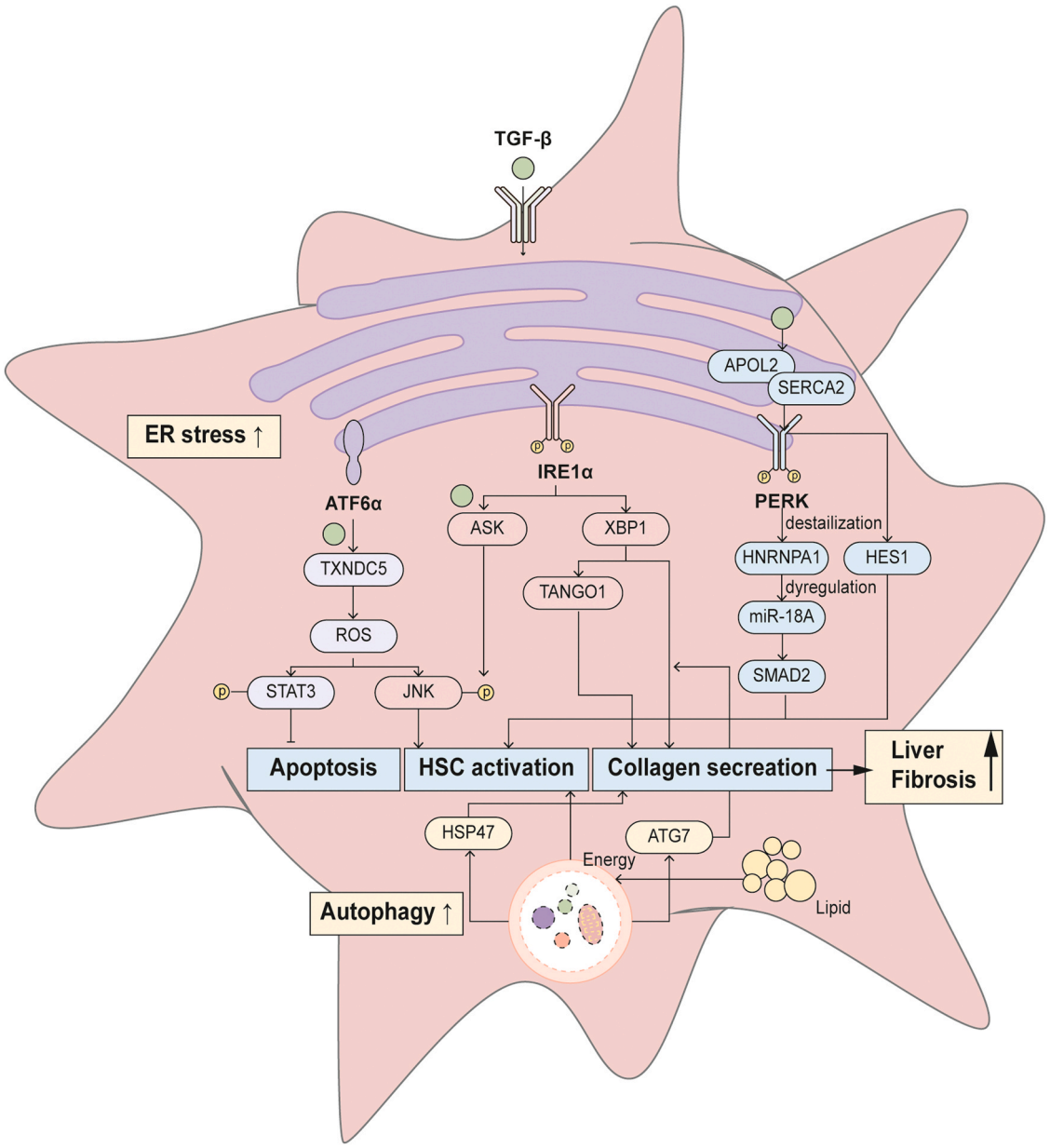


Fig. 4. Chronic ER stress in HSC. This figure illustrates the mechanism of chronic endoplasmic reticulum (ER) stress in hepatic stellate cells (HSCs). The diagram highlights various signaling pathways triggered by ER stress, including the IRE1α/XBP1, PERK, and ATF6 pathways. These pathways modulate the activation of HSCs, leading to increased collagen secretion and contributing to liver fibrosis. The figure also indicates the involvement of TGF-β, a key factor in HSC activation and fibrosis progression. Additionally, the diagram suggests that chronic ER stress can induce apoptosis and autophagy, further influencing cell fate and contributing to the pathogenesis of liver fibrosis.

liver fibrosis. During chronic liver injury, the activation of HSCs significantly increases the synthesis and secretion of ECM proteins, which triggers ER stress and induces the UPR. Concurrently, ER stress signaling promotes the upregulation of fibrogenic genes, enhances HSC activation, and stimulates autophagic activity, thereby exacerbating the development of liver fibrosis.

The three branches of UPR signaling, ATF6 has been identified as a pivotal driver of HSC activation[132]. ATF6 enhances HSC activation and suppresses apoptosis by upregulating thioredoxin domain containing 5 (TXNDC5), thereby promoting the progression of liver fibrosis. TXNDC5, an ER protein disulfide isomerase, has been implicated in fibrosis in the heart[133] and lungs[134]. Recent studies have demonstrated that TXNDC5 is significantly upregulated in both human and murine models of liver fibrosis, particularly in activated HSCs[135]. The pro-fibrotic mechanism of TXNDC5 involves TGF-β1-induced ER stress, which regulates ATF6 transcription and promotes TXNDC5 expression. Elevated TXNDC5 levels activate redox-dependent JNK and STAT3 pathways, enhancing HSC proliferation, activation, and ECM production while inhibiting apoptosis, thus driving the progression of liver fibrosis. Notably, HSC-specific deletion of TXNDC5 has been shown to reverse liver fibrosis in mice, underscoring its potential as a therapeutic target.

In addition to ATF6, the IRE1α-mediated signaling pathway plays an important role in regulating autophagy and activation of HSCs. Studies have demonstrated that inhibiting the IRE1α pathway significantly suppresses HSC activation and autophagic activity through a p38 MAPK-dependent mechanism, thereby alleviating fibrotic responses[136]. The downstream effector protein of IRE1α, XBP1, is closely associated with enhanced collagen secretion and autophagy. Overexpression of XBP1 induces excessive collagen type I production in HSCs via a

TGF-β1-independent mechanism; however, silencing the key autophagy regulator ATG7 (autophagy-related protein 7) effectively mitigates this effect[137]. Additionally, XBP1 regulates the expression of TANGO1 (Transport and Golgi Organization 1), which in turn influences collagen type I secretion. Loss of TANGO1 results in the retention of type I procollagen in the ER, activating UPR signaling and promoting HSC apoptosis[138]. These findings underscore the critical role of the IRE1α-XBP1 axis and its interplay with autophagy pathways in HSC activation and the progression of fibrosis. Furthermore, ATF6 collaborates with IRE1α to orchestrate the fibrogenic processes driven by HSCs [132]. This interplay underscores the intricate nature of the UPR signaling network and provides valuable insights into potential therapeutic targets for liver fibrosis.

The role of PERK in HSC activation remains incompletely understood. However, studies have shown that the PERK signaling pathway promotes HSC activation and liver fibrosis progression by modulating the instability of miR-18A and HNRNPA1[139]. Specifically, ER stress induces HNRNPA1 destabilization through the PERK pathway, leading to dysregulation of miR-18A. This dysregulation subsequently upregulates SMAD2 expression, driving fibrosis progression. These findings highlight the potential regulatory role of the PERK pathway in liver fibrosis. Recent studies have revealed that the APOL2-mediated PERK-HES1 pathway plays a crucial role in liver fibrosis development [140]. Mechanistically, under TGF-β1 stimulation, the expression of APOL2, an apolipoprotein enriched in the ER, is significantly upregulated. APOL2 binds to sarcoplasmic/ER calcium ATPase 2 (SERCA2), inducing ER stress and activating the PERK-HES1 signaling pathway, thereby driving fibrosis progression. Furthermore, targeting APOL2 with 12-deoxyphorbol 13-palmitate (DP) or knocking down APOL2 significantly suppresses the APOL2-SERCA2-PERK-HES1 signaling axis and mitigates fibrosis progression. Moreover, the expression of ATF4, a key transcription factor in ER stress within HSCs, is strongly associated with liver fibrosis[141]. Distinct from its classical role in regulating UPR genes under ER stress conditions, ATF4 promotes fibrosis by activating the transcription of epithelial-mesenchymal transition (EMT)-related genes during liver fibrosis. Specific deletion of ATF4 in HSCs significantly attenuates liver fibrosis. Furthermore, a small-molecule inhibitor targeting ATF4 translation has been shown to effectively alleviate liver fibrosis.

The JNK signaling pathway, as a downstream effector of ER stress, plays a key role in HSC activation and fibrosis. Notably, in HSCs, the loss of JNK1 shortens cell lifespan and reduces their differentiation capacity into myofibroblasts[142], indicating that JNK1 has a pro-fibrotic role in HSCs, making it a potential antifibrotic target.

The UPR alone is insufficient to effectively activate HSCs; instead, the synergistic interaction between ER stress and autophagy is critical for HSC activation and the progression of liver fibrosis. Autophagy supports HSC activation by breaking down lipid droplets to provide energy[143], and it plays an essential role in collagen maturation and HSC survival. HSP47, a collagen-specific molecular chaperone, is responsible for collagen maturation and secretion. In HSCs lacking HSP47, immature type I collagen precursors accumulate, a phenomenon exacerbated when autophagic function is impaired. This is accompanied by increased expression of ER stress markers such as Bip and Grp94, activation of CHOP, and intensified ER stress, ultimately leading to HSC apoptosis[144]. Furthermore, the knockdown of the autophagy-related protein ATG7 suppresses XBP1-mediated type I collagen expression, underscoring the pivotal role of autophagy in the regulation of liver fibrosis[137].

4.3. Chronic ER stress in kupffer cell

Kupffer cells are the predominant resident macrophages in the liver, playing a crucial role in maintaining hepatic immune homeostasis, regulating inflammatory responses, and driving fibrosis progression. Recent studies have shown that the activation of ER stress in Kupffer cells has significant implications for the onset and progression of liver diseases. However, the precise mechanisms by which ER stress mediates Kupffer cells inflammatory polarization and contributes to liver fibrosis remain incompletely understood. Existing research suggests that the activation of ER stress in Kupffer cells, particularly through the IRE1α signaling pathway, plays a pivotal role in inflammation and is closely linked to HSC activation.

ER stress represents an important link between hepatocellular injury and liver inflammation[5]. ER stress, and the IRE1α-XBP1 pathway in particular, is an important regulator in inflammatory macrophage activation[145,146]. Indeed, in several murine models of fibrosis, myeloid-specific deletion of Xbp1 led to improved liver histology and a shift toward restorative macrophage phenotypes, mediated by reduced activation of the NOD-, LRR-, and NLRP3 inflammasome pathway[147, 148]. Future studies will need to investigate the contribution of the PERK and ATF6 branches of the ER stress response to macrophage activation in liver fibrosis. Excessive activation of IRE1α can drive the pro-inflammatory response of Kupffer cells, amplifying inflammatory signaling and exacerbating liver injury and fibrosis progression. Studies have demonstrated that IRE1α mediates the activation of the NLRP3 inflammasome, promoting the secretion of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 by Kupffer cells[149]. This process induces M1 polarization of Kupffer cells, further aggravating liver damage [150].

In vitro experiments have shown that the ERS inhibitor 4-PBA effectively suppresses the pro-inflammatory polarization of bone marrow-derived macrophages (BMDMs)[150]. Additionally, IRE1α knockdown inhibits M1 polarization and promotes M2 phenotype transformation[150]. Pharmacological inhibition of IRE1α RNase activity has been found to mitigate Kupffer cell-mediated inflammation, thereby improving ischemia/reperfusion injury (IRI) [149]. In the context of fatty liver disease, excessive activation of IRE1α in Kupffer cells further exacerbates IRI and ROS production[150], suggesting that IRE1α could be a potential therapeutic target for regulating fatty liver-related IRI.

Triggering receptor expressed on myeloid cells 1 (TREM-1) is a key receptor that amplifies inflammatory signaling and plays a central role in the pro-inflammatory response of Kupffer cells. TREM-1 is highly expressed in Kupffer cells and monocytes and has been shown to aggravate liver injury and fibrosis progression in murine models of chronic liver damage by promoting pro-inflammatory cytokine release and immune cell mobilization[151]. Studies have revealed that TREM-1 modulates the pro-inflammatory response of Kupffer cells via the ER stress pathway. Its activation induces the expression of ER stress markers (ATF6, PERK, IRE1α, and XBP-1s) and upregulates IL-1β, TNF-α, and IL-6 levels. Inhibition of ER stress or the IRE1α/XBP-1s pathway effectively reduces TREM-1-mediated inflammation. Furthermore, the TREM-1 signaling inhibitor LR12 has been shown to reduce LPS-induced ER stress, further confirming the critical role of TREM-1 in shaping the pro-inflammatory microenvironment mediated by Kupffer cell ER stress [152]. These findings suggest that TREM-1 may serve as a potential therapeutic target for hepatitis and liver fibrosis, and modulation of its signaling pathway could provide novel therapeutic strategies for fibrosis and other inflammatory liver diseases.

Beyond regulating inflammatory responses, ER stress activation in Kupffer cells is also closely associated with liver fibrosis resolution. Studies have indicated that ER stress in Kupffer cells promotes the clearance of apoptotic-activated HSCs, thereby accelerating fibrosis regression. During this process, ERS induces Kupffer cell M1 polarization and upregulates TNF expression, which, via the TNF-R1–caspase 8 pathway, facilitates HSC apoptosis. This mechanism unveils a previously unrecognized role of Kupffer cells in fibrosis resolution and offers potential intervention strategies to promote fibrosis regression[153].

Nogo-B (Reticulon 4B, RTN4B) is an ER-resident protein that regulates ER structure and function and may serve as a potential Kupffer cell target in alcoholic liver disease (ALD) treatment. Studies have shown

that Nogo-B influences the development of ALD by modulating the M1/M2 polarization of Kupffer cells. In both ALD patients and murine models, Nogo-B expression levels correlate positively with disease severity. Nogo-B promotes M1 polarization of Kupffer cells, while its deficiency enhances ER stress and favors M2 polarization. Notably, Nogo-B knockout mice exhibit reduced liver injury and steatosis following chronic ethanol feeding, suggesting that Nogo-B may exacerbate liver damage by enhancing M1 polarization and could be a potential target for ALD therapy[154].

In conclusion, ER stress activation in Kupffer cells plays a crucial role in liver fibrosis, inflammatory responses, and liver injury repair, involving multiple key signaling pathways such as IRE1α, TREM-1, and Nogo-B. These findings highlight the complex role of Kupffer cells in the pathogenesis of liver diseases and provide new potential therapeutic targets for liver fibrosis and related disorders.

5. Target the UPR for liver fibrosis treatment

Currently, there is a lack of effective pharmacological treatments for liver fibrosis. Given that chronic ER stress plays a causative role in the course of hepatic fibrosis, developing therapeutic strategies to modulate maladaptive UPR is of significant clinical importance.

5.1. Small molecules targeting ER stress

Small molecules targeting different branches of the UPR have shown promising potential in alleviating ER stress and may serve as effective therapeutic candidates for liver fibrosis treatment. Table 3 provides a summary of these molecules and their mechanisms of action.

5.1.1. Misfolded proteins

Azoramide is an orally bioavailable small-molecule UPR modulator that enhances ER protein-folding capacity and improves the function of ER chaperones such as Bip[155,156]. By reducing the accumulation of misfolded proteins, azoramide alleviates ER stress and has demonstrated antidiabetic activity by improving insulin resistance. These properties make azoramide a promising therapeutic candidate for MASH and other ER stress-related metabolic disorders[155,156].

5.1.2. IRE1

IRE1α is the most evolutionarily conserved sensor of the UPR and plays a pivotal role in the onset and progression of liver diseases. Its dual functionality—kinase and RNase activities—is critical for cellular adaptation to ER stress. As discussed in previous sections, excessive activation of IRE1α can drive apoptosis, inflammatory responses, and metabolic disorders, whereas its moderate inhibition has been shown to mitigate liver injury. Consequently, modulating IRE1α activity presents a promising therapeutic avenue for liver disease treatment. To date, a variety of small-molecule inhibitors have been developed to target IRE1α, which can be broadly categorized into RNase inhibitors and kinase inhibitors[157]. RNase inhibitors primarily interact with the catalytic center of the IRE1α RNase domain, thereby suppressing its RNA cleavage activity, preventing XBP1 mRNA splicing, and inhibiting the UPR. A notable class of RNase inhibitors contains a salicylaldehyde pharmacophore, which forms a Schiff base with the RNase active site, effectively blocking its activity[158]. Representative RNase inhibitors include STF083010[159] and 4μ8c[160,161], with 4μ8c being widely used in fundamental research due to its high selectivity. Additionally, the MKC series of inhibitors represents another important group of RNase inhibitors. MKC-3946 was one of the earliest IRE1α RNase inhibitors developed and has been used to study the role of IRE1α in disease models[162,163]. MKC-8866, an optimized version of MKC-3946, exhibits improved selectivity and pharmacokinetic properties. It has shown promising therapeutic potential in preclinical studies for breast and prostate cancers and has entered Phase I clinical trials[164,165]. MKC-9989, a novel RNase inhibitor, is still in its early stages of research [166].

These aldehyde-containing inhibitors of IRE1α RNase have shown promising pharmacological properties in vitro. At micromolar concentrations, they can fully inhibit XBP1 splicing and RIDD activity without exhibiting cytotoxicity in cultured cells[167]. Moreover, they demonstrate high target specificity with minimal effects on related RNase L activity[161,166]. However, these advantages do not fully translate in vivo. Due to the inherent chemical reactivity of the aldehyde group, these compounds may interact nonspecifically with other proteins or small molecules, leading to off-target effects — a concern particularly pronounced with 4μ8 C[168]. Furthermore, studies have shown that in IRE1-dependent tumor models in mice, effective suppression of IRE1 signaling requires very high doses of these inhibitors[159]. This suggests that these compounds suffer from poor pharmacokinetic properties, such as low bioavailability and rapid metabolism. Therefore, despite their encouraging in vitro profiles, further optimization is necessary to improve the stability, specificity, and in vivo efficacy of these aldehyde-based RNase inhibitors before clinical translation can be realized.

Unlike RNase inhibitors, kinase inhibitors primarily target the ATP-binding pocket of the IRE1α kinase domain, thereby modulating its RNase activity[157]. Based on their effects on RNase activity, kinase inhibitors can be further categorized into Type 1 kinase inhibitors (partial RNase agonists) and Type 2 kinase inhibitors (RNase inhibitors) [169]. Type 1 kinase inhibitors competitively bind to the ATP-binding pocket, leading to IRE1α dimerization and partial activation of RNase activity, even in the absence of ER stress[158]. Representative compounds include APY29[170], a non-specific IRE1α inhibitor, and Sunitinib[171,172], a broad-spectrum tyrosine kinase inhibitor. In contrast, Type 2 kinase inhibitors stabilize the inactive conformation of the IRE1α kinase, binding to a hydrophobic pocket adjacent to the ATP-binding site, thereby blocking RNase activity[158]. The most well-known inhibitors in this category are kinase-inhibiting RNase attenuators (KIRAs), including KIRA3, KIRA6, KIRA7, and KIRA8, with KIRA8 exhibiting the highest selectivity[158,173,174]. Additionally, B-I09 inhibits RNase activity indirectly by preventing IRE1α dimerization[175,176].

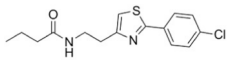
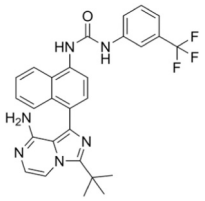
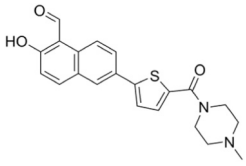
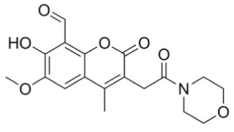
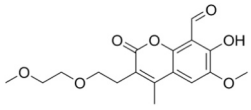
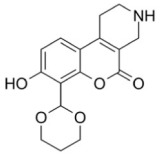
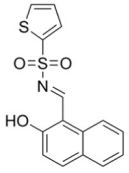
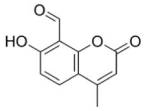
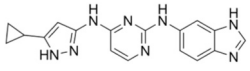
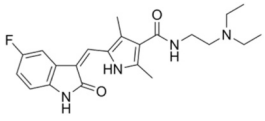
In conclusion, IRE1α plays a critical role in ER stress regulation and liver disease pathogenesis. Small-molecule inhibitors targeting IRE1α have shown significant potential in both basic and preclinical research. Further investigation into the mechanisms and pharmacokinetics of these inhibitors may lead to novel therapeutic strategies for liver fibrosis.

5.1.3. PERK

PERK is a key sensor of the UPR, primarily functioning to phosphorylate eIF2α and attenuate global protein synthesis, thereby alleviating ER stress. However, excessive activation of the PERK pathway can lead to chronic ER stress, apoptosis, and the progression of multiple diseases. Therefore, modulating PERK activity has emerged as a potential therapeutic strategy. The currently available small-molecule compounds can be broadly classified into PERK kinase inhibitors and eIF2α phosphorylation modulators, with the latter further intersecting with the integrated stress response (ISR) [177] pathway.

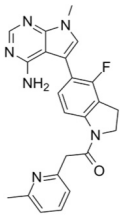
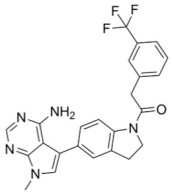
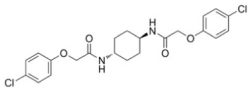
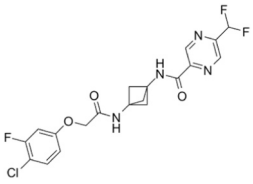
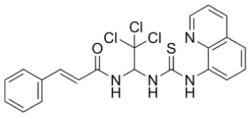
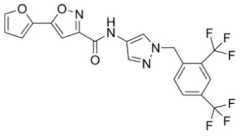
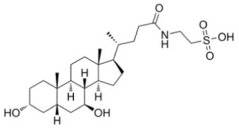
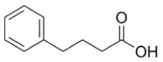
PERK kinase inhibitors act by competitively binding to the ATP pocket of PERK, thereby blocking its kinase activity and preventing eIF2α phosphorylation. GSK2606414[178,179] and its fluorinated analog, GSK2656157[180–182], are among the earliest potent PERK kinase inhibitors, effectively suppressing eIF2α phosphorylation under ER stress conditions and primarily explored for cancer therapy. However, given the potential side effects of PERK inhibition, such as pancreatic toxicity, further optimization is necessary for clinical applications. In contrast, eIF2α phosphorylation modulators regulate the phosphorylation status of eIF2α to influence protein translation. Salubrinal[183–185] and its derivatives, Guanabenz and Sephin-1[186,187], function by inhibiting eIF2α dephosphorylation, thereby

Table 3
Small molecules targeting UPR branches.

Target Objects	Molecules	Structure	Mechanism	Status	Ref
Misfolded Proteins	Azoramide		UPR modulator and ER stress protector		[155,156]
IRE1-α	KIRA6		Type II kinase inhibitor	Preclinical development	[170,173, 174]
	MKC−3946		RNase domain	Tool compound	[162,163, 212]
	MKC−8866		RNase domain	Tool compound	[164,165]
	MKC−9989		RNase domain	Tool compound	[166]
	B-I09 (4μ8 C analogue)		IRE1 RNase Inhibitor	Tool compound	[175,176]
	STF−083010		RNase domain	Tool compound	[159]
	4μ8c		RNase domain	Tool compound	[160,161]
	APY29		Type I kinase inhibitor; inhibits IRE1-ASK1 pathway	Tool compound	[170]
	Sunitinib		Type I kinase inhibitor; inhibits receptor tyrosine kinases	In clinical use	[171,172]

(*continued on next page*)

Table 3 (*continued*)

Target Objects	Molecules	Structure	Mechanism	Status	Ref
PERK-eIF2α	GSK2656157		ATP-binding site	Tool compound; RIPK inhibitor IC50 = 1.9 μM	[180–182]
	GSK2606414		Type I kinase inhibitor, type II features	Tool compound; RIPK inhibitor IC50 = 7.3 μM	[178,179]
eIF2α	ISRIB		Activators stabilizing eIF2B	Preclinical development	[191]
	2BAct		Stabilizes eIF2B	Tool compound	[213]
	Salubrinal		eIF2α dephosphorylation inhibitor	Tool compound; weak effect on purified PPP1R15A	[183–185]
ATF6	Ceapins		Tethers ATF6 cytosolic domain and ABCD3	Tool compound; does not affect ABCD3 function	[193]
Others	TUDCA		Hydrophobic chemical chaperone; anti-inflammatory effects that reduce misfolding-associated damage; acts as a ligand for FXR and TGR5 receptors	Clinical trials performed in amyotrophic lateral sclerosis (e.g. NCT03800524)	[196,197]
	4-PBA		Hydrophobic chemical chaperone; binds and stabilizes misfolded proteins; inhibits HDACs; reduces ER quality control	Clinical trials performed in cystic fibrosis (e.g. NCT00590538 and NCT00016744)	[198,214]

prolonging its phosphorylated state and enhancing cellular resilience to ER stress.

Salubrinal was initially identified in in vitro screens as a compound capable of protecting cells from tunicamycin-induced ER stress by increasing phosphorylation of eIF2α[188]. However, subsequent studies reported that Salubrinal did not significantly inhibit eIF2α dephosphorylation in vitro, even at high concentrations, and often caused protein precipitation, suggesting poor target specificity[189]. These limitations significantly constrain its potential for clinical translation. Guanabenz, an FDA-approved antihypertensive agent, was later found to enhance the ISR by increasing eIF2α phosphorylation. Its mechanism of action is believed to involve selective binding to PPP1R15A, thereby preventing eIF2α dephosphorylation. Cells deficient in PPP1R15A or PPP1R15B exhibited heightened sensitivity to Guanabenz, further supporting its proposed specificity[187]. Nevertheless, Guanabenz's sedative and hypotensive side effects restrict its use as an ISR modulator in clinical settings. Instead, its primary value lies in serving as a chemical scaffold for the development of safer and more selective derivatives. Sephin1, a non-sedating derivative of Guanabenz that lacks affinity for α2-adrenergic receptors, has shown improved safety profiles. It has been reported to selectively disrupt the PPP1R15A–PP1 complex and mimic the protective effects of PPP1R15A deficiency in mouse models of peripheral neuropathy caused by protein misfolding[186,190]. Some studies further demonstrated that Sephin1 can inhibit dephosphorylation of eIF2α by recombinant PPP1R15A–PP1 complexes in vitro. However, these findings have not been universally

reproducible, and additional research has shown that Sephin1 retains activity in PPP1R15A-deficient or eIF2αS51A mutant cells, where phosphorylation and dephosphorylation cannot occur[189]. These results suggest potential off-target effects or alternative mechanisms of action. Therefore, its translational potential remains to be fully validated through comprehensive investigation.

On the other hand, ISRIB is an ISR inhibitor that binds to eIF2B, facilitating the formation of its complex even in the presence of high P-eIF2α levels, thereby restoring protein translation and suppressing the ATF4-mediated stress response[191]. Additionally, Dibenzoylmethane and Trazodone have been shown to restore protein translation without altering eIF2α phosphorylation levels, providing a potential neuroprotective strategy[192].

Overall, the regulation of PERK and its downstream eIF2α signaling pathway holds significant therapeutic potential across multiple diseases. While PERK kinase inhibitors have shown promise in cancer research, their selectivity and safety profiles require further optimization. Conversely, eIF2α phosphorylation modulators offer a more nuanced intervention strategy, particularly in MASH and liver fibrosis. Future research should focus on optimizing the pharmacokinetic properties of these small molecules and exploring their precise mechanisms in various liver diseases.

5.1.4. ATF6

Currently, research on ATF6 as a therapeutic target remains limited. However, its role in the UPR highlights its potential in drug development. Ceapins, a class of ATF6 inhibitors, effectively block its translocation from the ER to the Golgi apparatus, thereby suppressing downstream signaling[193]. In contrast, activators such as Compound 147 and Compound 263 enhance ATF6-mediated stress responses[194,195]. Although ATF6-targeted modulation is still in its early stages, the identification of these small molecules offers promising avenues for future liver disease therapeutics.

5.1.5. Chemical chaperones

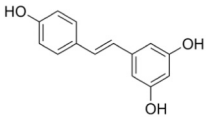
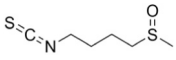
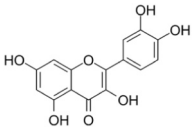
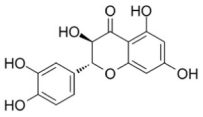
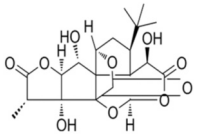
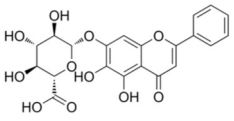
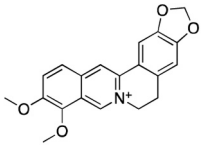
Chemical chaperones play a pivotal role in alleviating ER stress by enhancing protein-folding capacity and preserving cellular homeostasis. Among them, tauroursodeoxycholic acid (TUDCA) and 4-phenylbutyric acid (4-PBA) are well-characterized compounds. TUDCA has been shown to mitigate ER stress-induced apoptosis and mitochondrial depolarization, while also improving insulin sensitivity in both the liver and skeletal muscle in a HFD-induced MASLD mouse model and a clinical study involving 20 obese individuals[196,197]. 4-PBA, an FDA-approved treatment for urea cycle disorders, functions as a hydrophobic chaperone that stabilizes misfolded proteins and prevents their aggregation[198]. Additionally, it has demonstrated clinical efficacy in treating cystic fibrosis[199]. These findings underscore the therapeutic potential of chemical chaperones in targeting ER stress-associated liver fibrosis.

5.2. Natural compounds targeting ER stress and UPR

Natural compounds have also emerged as promising candidates for modulating UPR pathways and alleviating ER stress in liver fibrosis. Resveratrol[200,201], sulforaphane[202], quercetin[203], dihydroquercetin[204], ginkgolide B[205], baicalin[206,207], and berberine[208,209] have all been reported to exhibit ER stress-modulating properties. Table 4 provides an overview of these natural compounds and their potential roles in alleviating ER stress in liver fibrosis. These compounds exert diverse mechanisms of action, including antioxidant, anti-inflammatory, and ER stress-alleviating effects, making them attractive therapeutic options for liver fibrosis-related diseases.

Collectively, targeting the UPR represents a promising therapeutic strategy for liver fibrosis. Small molecules and natural compounds capable of modulating different branches of the UPR have demonstrated potential in alleviating ER stress and its pathological consequences. Further studies are required to elucidate their precise mechanisms of action and validate their therapeutic efficacy in preclinical and clinical settings.

Table 4
Natural compounds.

Natural Compounds	Structure	Mechanism	Ref
Resveratrol		Antioxidant, anti-inflammatory	[200]
Sulforaphane		Induces phase II detoxification enzymes, reduces inflammation	[202]
Quercetin		Antioxidant, modulates inflammatory pathways	[203]
Dihydroquercetin		Antioxidant, improves endothelial function	[204]
Ginkgolide B		Inhibits platelet aggregation, modulates vascular tone	[205]
Baicalin		Antioxidant, anti-inflammatory	[206, 207]
Berberine		Modulates glucose and lipid metabolism, anti-inflammatory	[208, 209]

6. Conclusion

ER stress plays a crucial role in the initiation and progression of liver fibrosis. Through the IRE1, PERK, and ATF6 signaling pathways, ER stress regulates hepatocyte survival and apoptosis, and influences inflammatory responses, oxidative stress, and HSC activation. Studies have shown that excessive or prolonged ER stress promotes HSC transdifferentiation, maintaining them in a pro-fibrotic state and thereby exacerbating liver fibrosis. Targeting ER stress-related signaling pathways and modulating the UPR may offer novel therapeutic interventions for liver fibrosis. However, most current studies are still conducted in animal models, with limited validation in human clinical trials. Furthermore, the precise molecular mechanisms linking ER stress to liver fibrosis are not yet fully understood. Future research should integrate multi-omics approaches and advanced single-cell technologies to elucidate these mechanisms more comprehensively. Additionally, to minimize off-target effects on other organs and preserve essential UPR functions, strategies for precisely modulating UPR activity require

further refinement to develop safer and more effective antifibrotic therapies.

Author's contributions

Yawei Kong, Zhengyang Chen, and Zhengtian Nie drafted the manuscript. Wei Chen provided critical feedback and overall guidance. Yawei Kong and Wei Chen revised the manuscript. All authors read and approved the final version of the manuscript.

CRediT authorship contribution statement

Yawei Kong: Writing – review & editing, Writing – original draft. **Zhengyang Chen:** Writing – review & editing. **Zhentian Nie:** Writing – review & editing. **Wei Chen:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition.

Declaration of Competing Interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

No data was used for the research described in the article.

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